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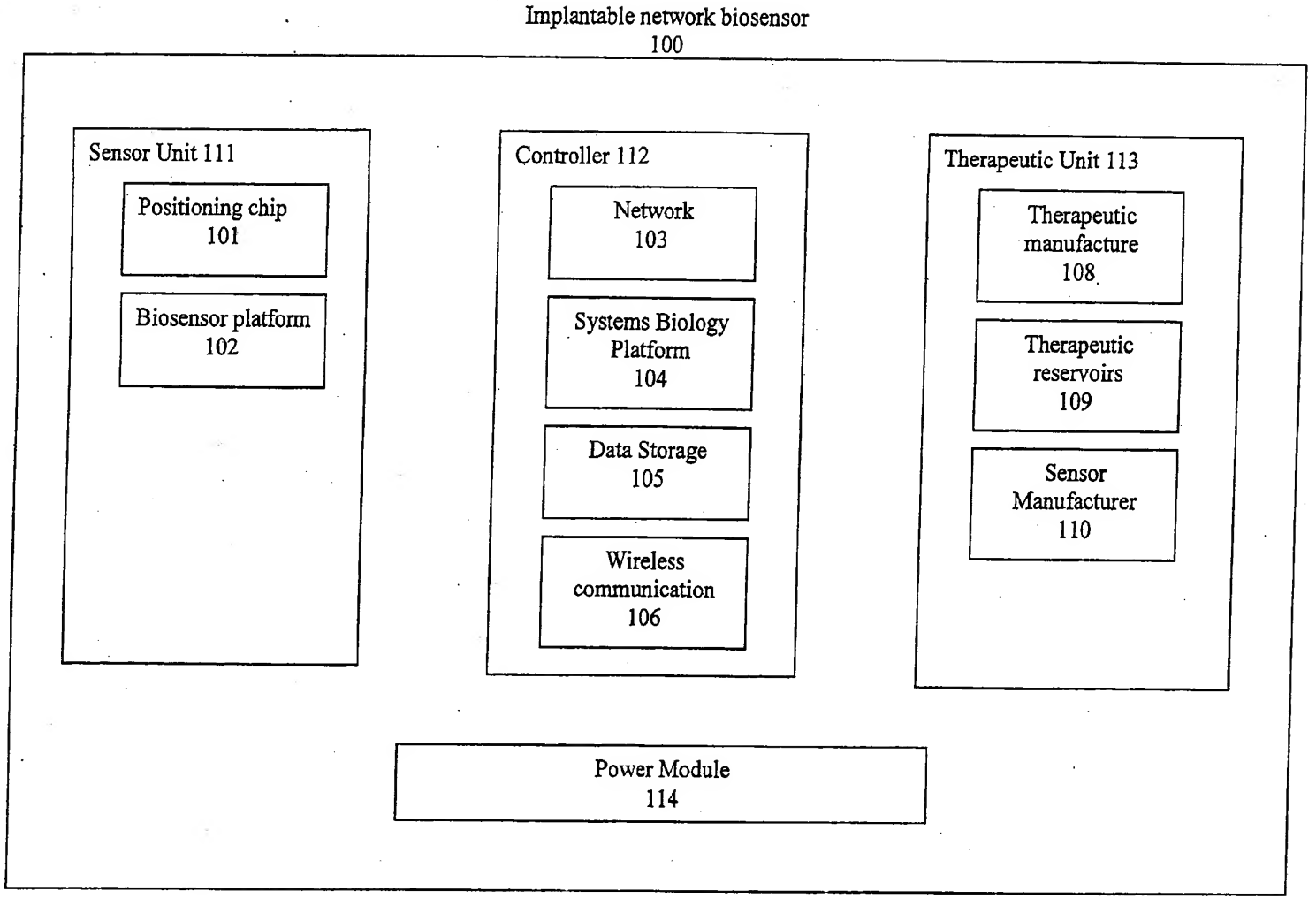

Implantable network biosensor
100
Sensor Unit 111
Positioning chip
101
Biosensor platform
102
Controller 112
Network
103
Systems Biology
Platform
104
Data Storage
105
Wireless
communication
106
Therapeutic Unit 113
Therapeutic
manufacture
108
Therapeutic
reservoirs
109
Sensor
Manufacturer
110
Power Module
114

Figure 1a

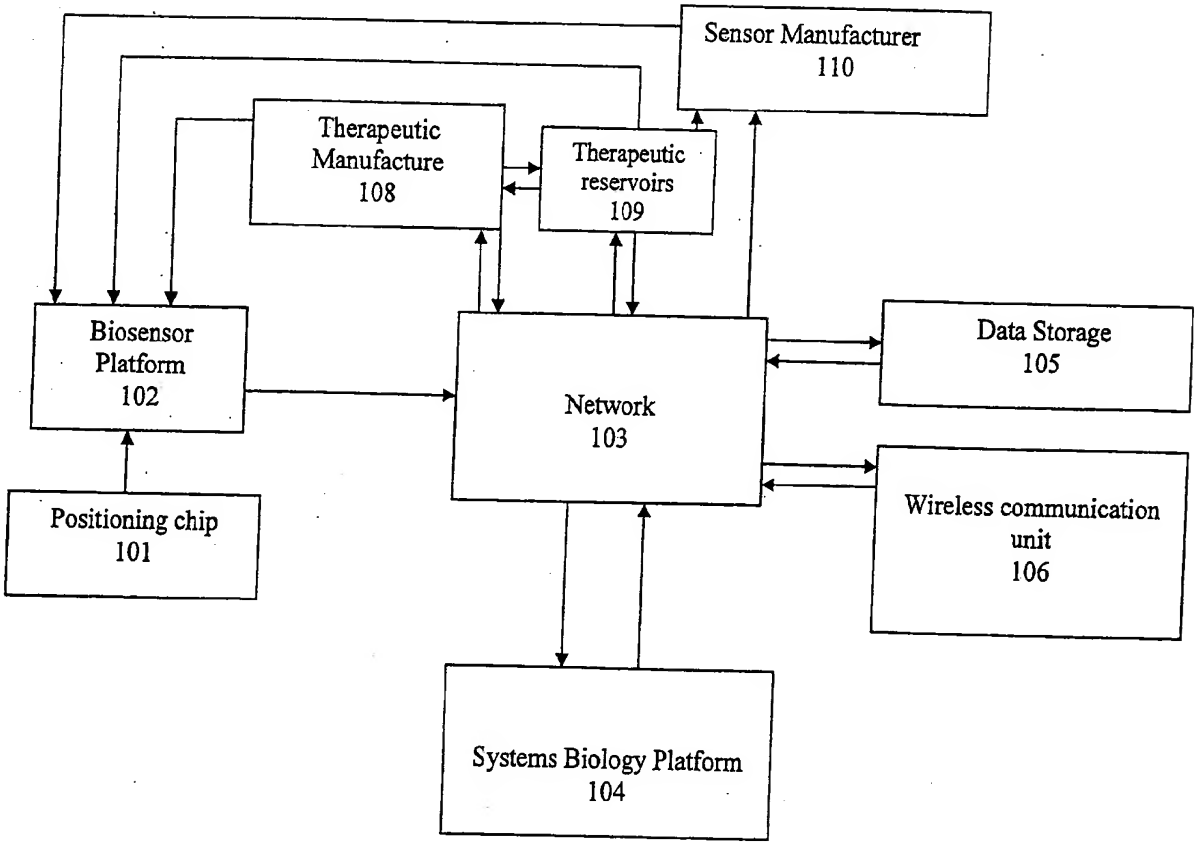

Sensor Manufacturer
110
Therapeutic
Manufacture
108
Therapeutic
reservoirs
109
Biosensor
Platform
102
Network
103
Data Storage
105
Positioning chip
101
Wireless communication
unit
106
Systems Biology Platform
104

Figure 1b

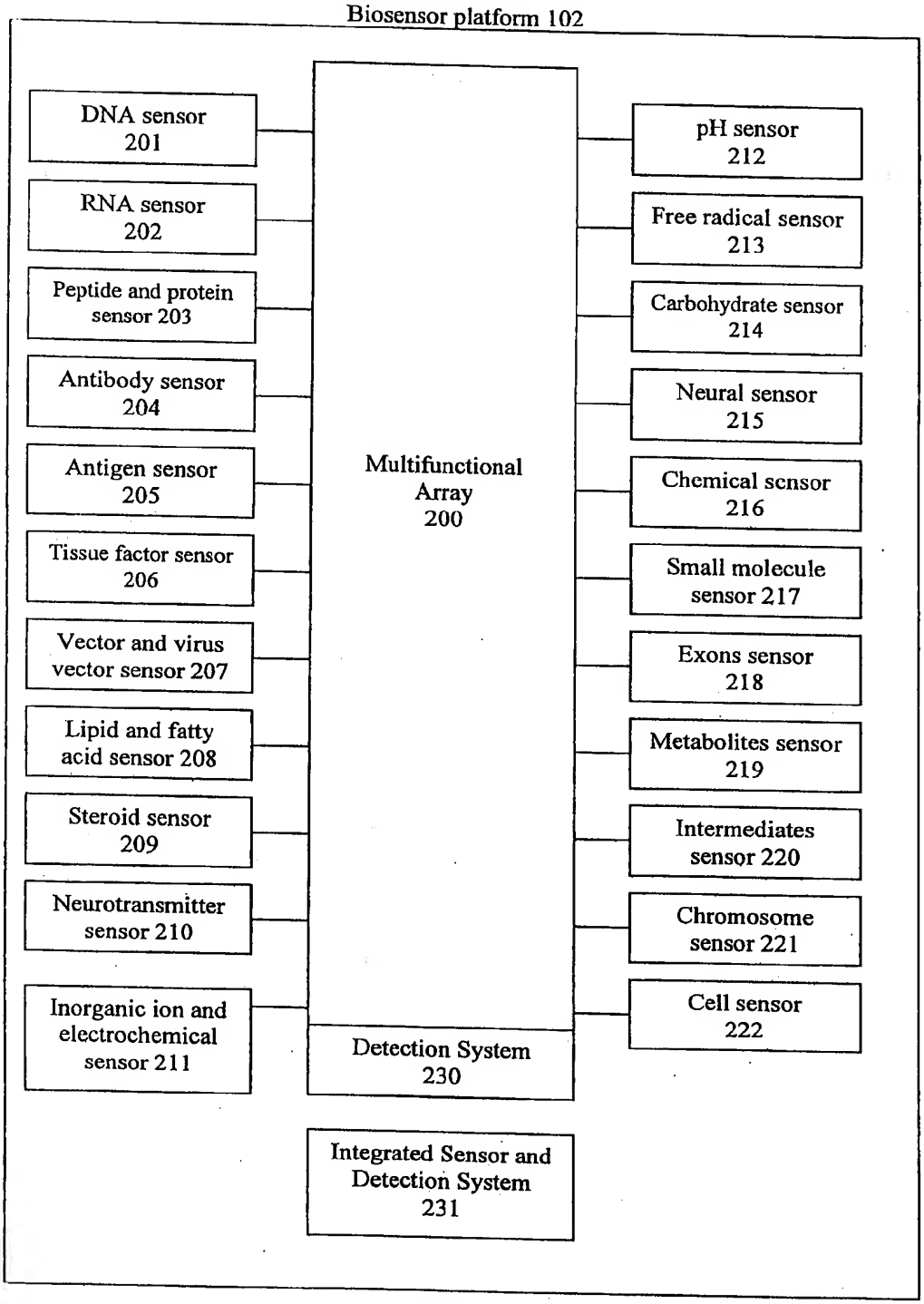

Biosensor platform 102
DNA sensor 201
RNA sensor 202
Peptide and protein sensor 203
Antibody sensor 204
Antigen sensor 205
Tissue factor sensor 206
Vector and virus vector sensor 207
Lipid and fatty acid sensor 208
Steroid sensor 209
Neurotransmitter sensor 210
Inorganic ion and electrochemical sensor 211
Multifunctional Array 200
Detection System 230
Integrated Sensor and Detection System 231
pH sensor 212
Free radical sensor 213
Carbohydrate sensor 214
Neural sensor 215
Chemical sensor 216
Small molecule sensor 217
Exons sensor 218
Metabolites sensor 219
Intermediates sensor 220
Chromosome sensor 221
Cell sensor 222

Figure 2

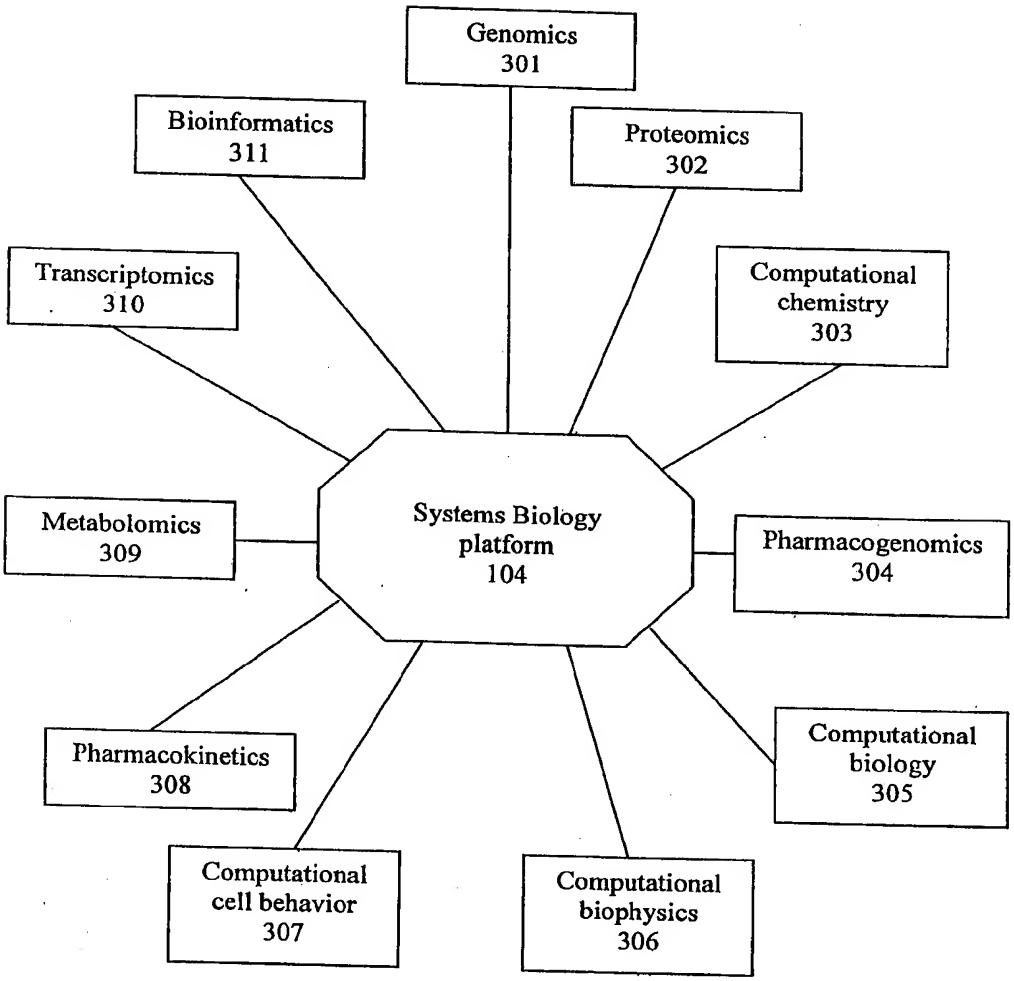

Genomics
301
Bioinformatics
311
Proteomics
302
Transcriptomics
310
Computational
chemistry
303
Systems Biology
platform
104
Metabolomics
309
Pharmacogenomics
304
Pharmacokinetics
308
Computational
biology
305
Computational
cell behavior
307
Computational
biophysics
306

Figure 3a

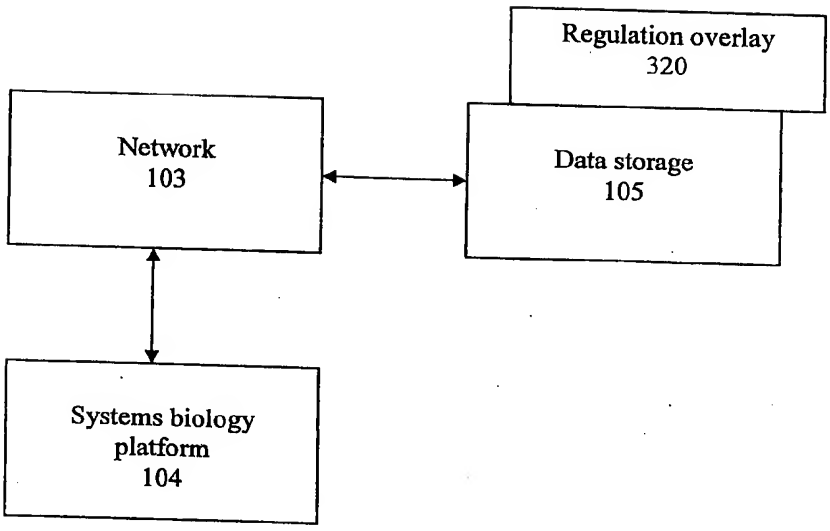

Regulation overlay
320
Network
103
Data storage
105
Systems biology
platform
104

Figure 3b

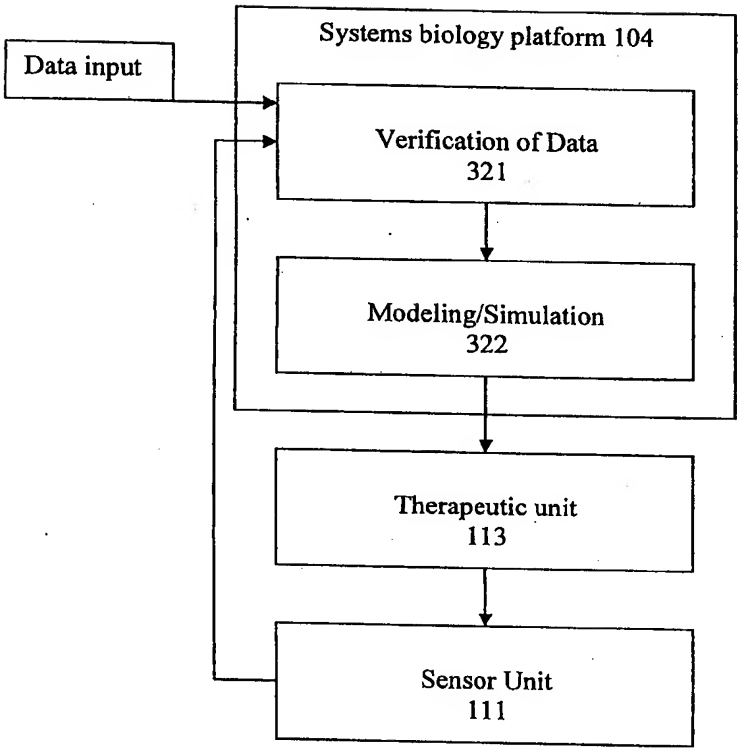

Systems biology platform 104
Data input
Verification of Data
321
Modeling/Simulation
322
Therapeutic unit
113
Sensor Unit
111

Figure 3c

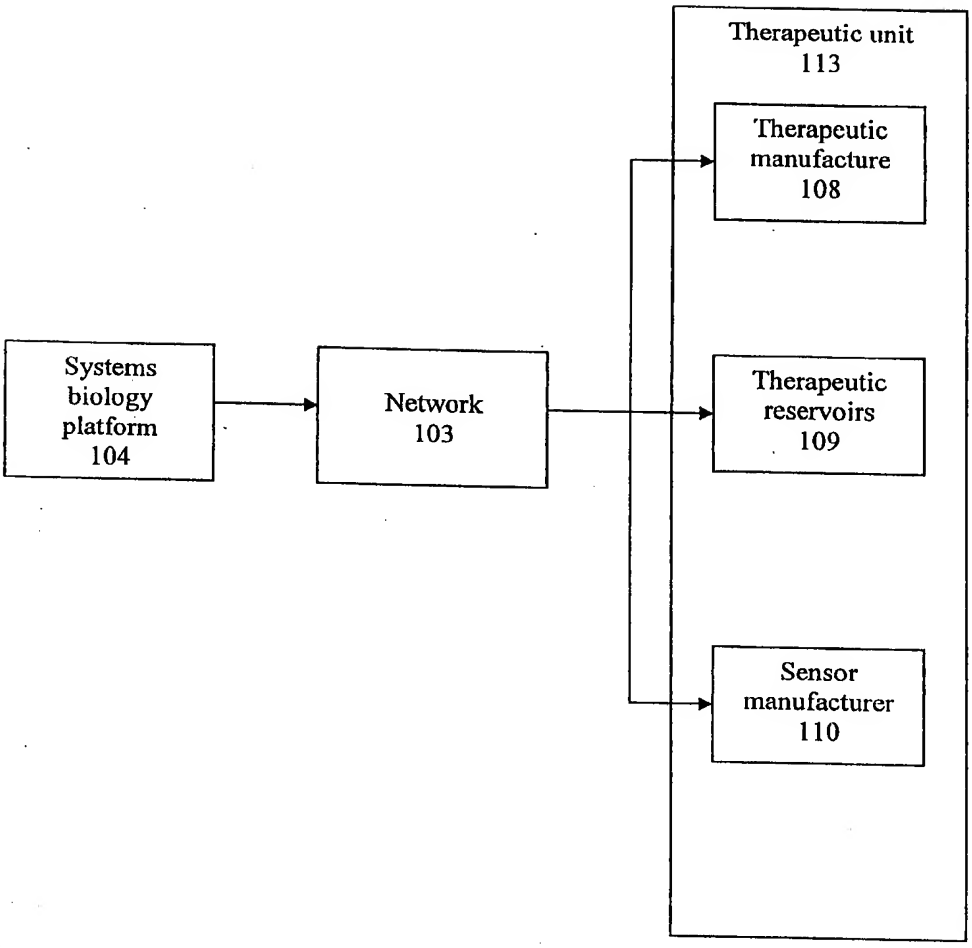

Therapeutic unit
113
Therapeutic manufacture
108
Systems biology platform
104
Network
103
Therapeutic reservoirs
109
Sensor manufacturer
110

Figure 4a

Therapeutic Manufacture 108

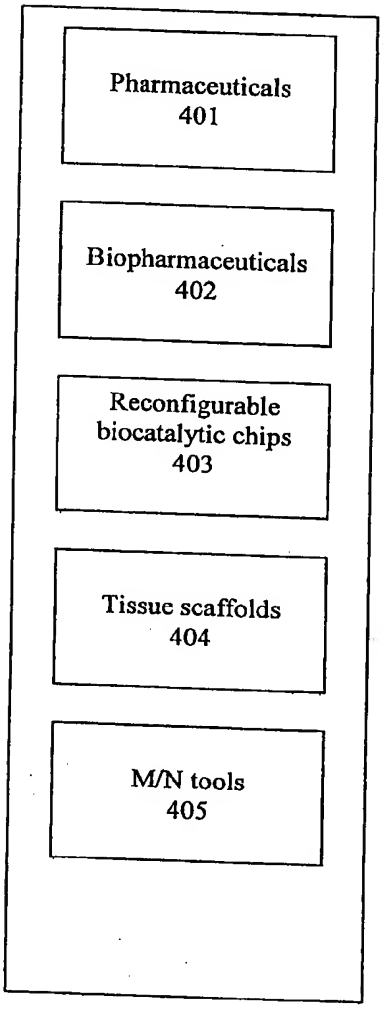


Figure 4b

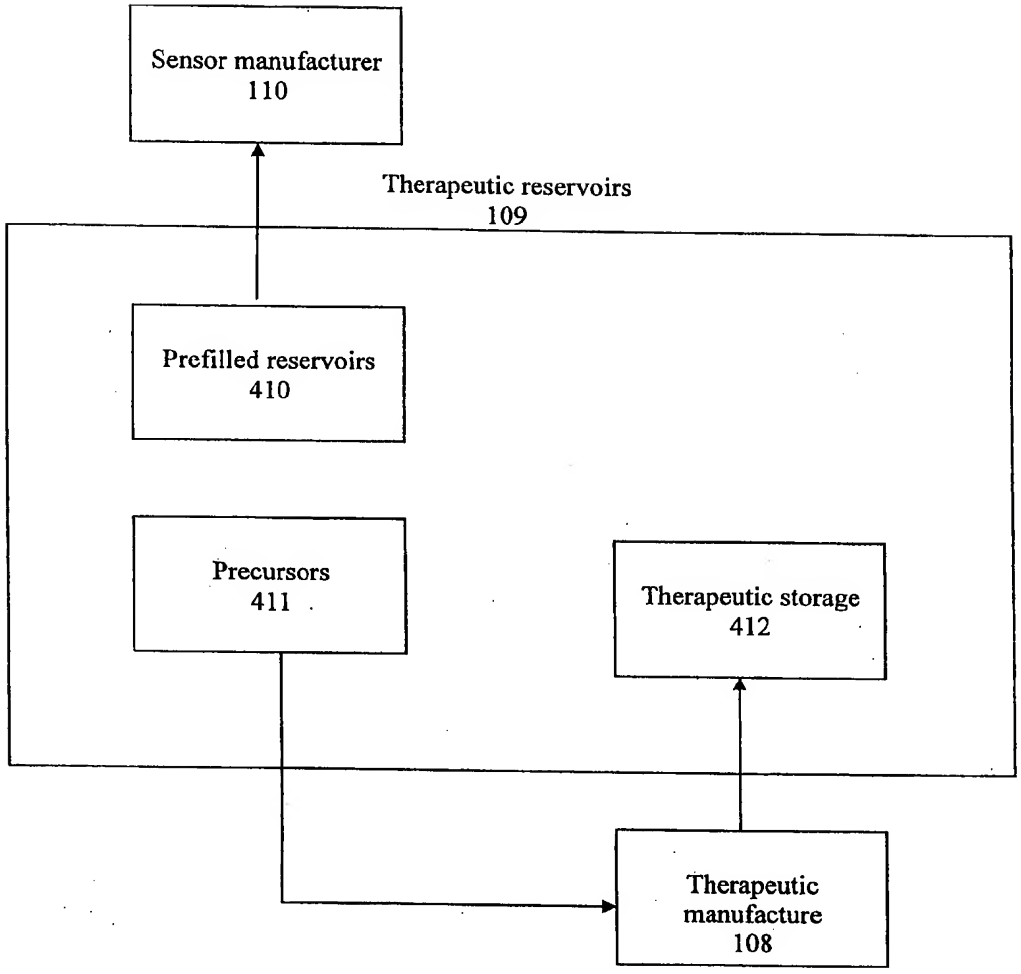

Sensor manufacturer
110
Therapeutic reservoirs
109
Prefilled reservoirs
410
Precursors
411
Therapeutic storage
412
Therapeutic
manufacture
108

Figure 4c

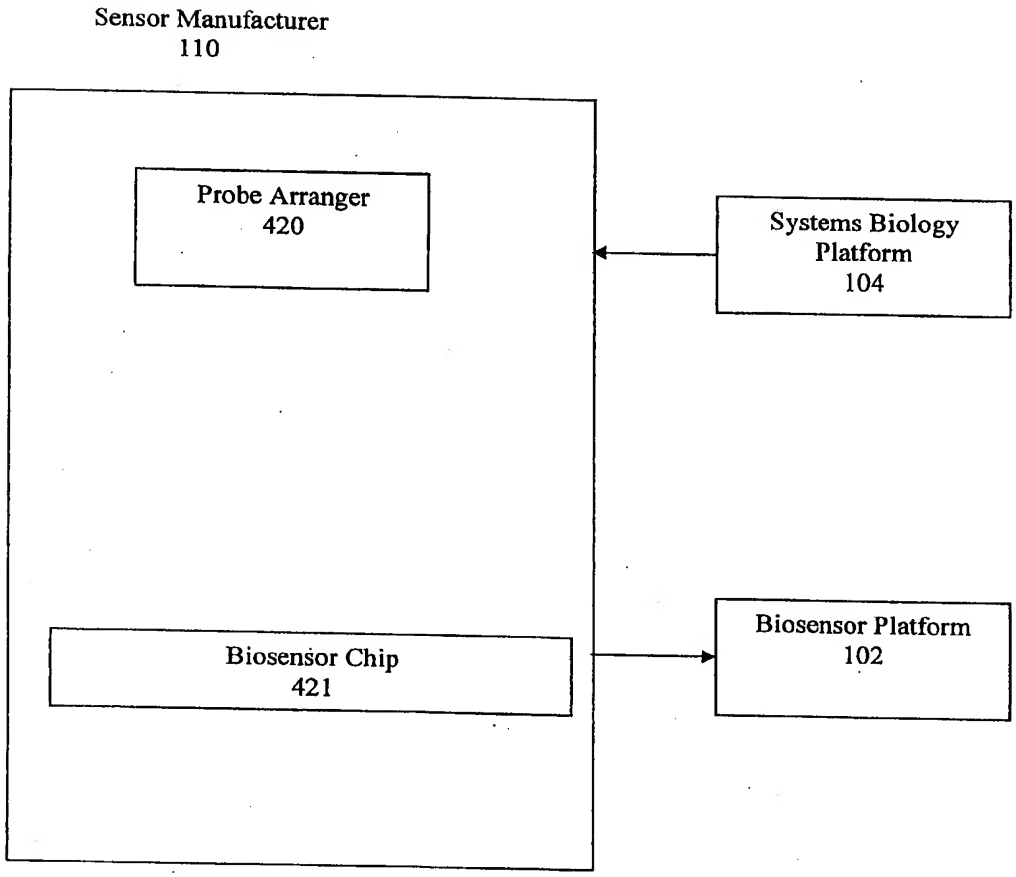

Sensor Manufacturer
110
Probe Arranger
420
Systems Biology
Platform
104
Biosensor Chip
421
Biosensor Platform
102

Figure 4d

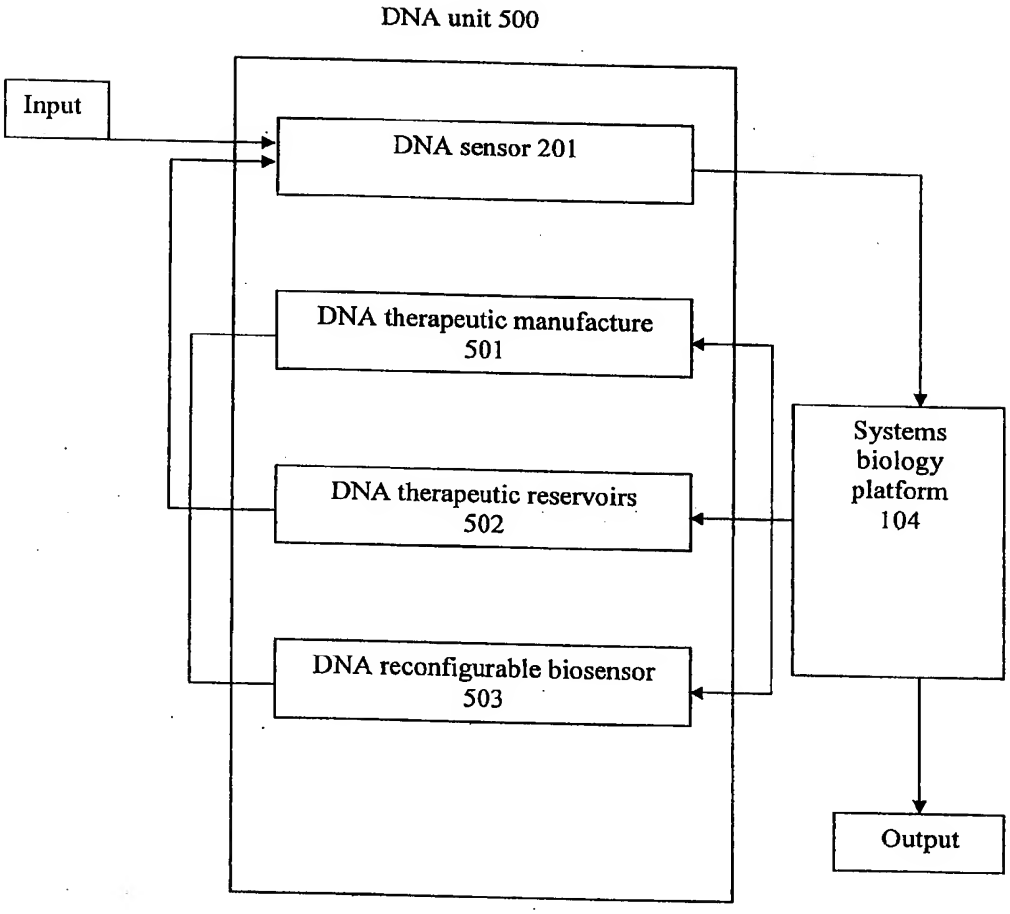
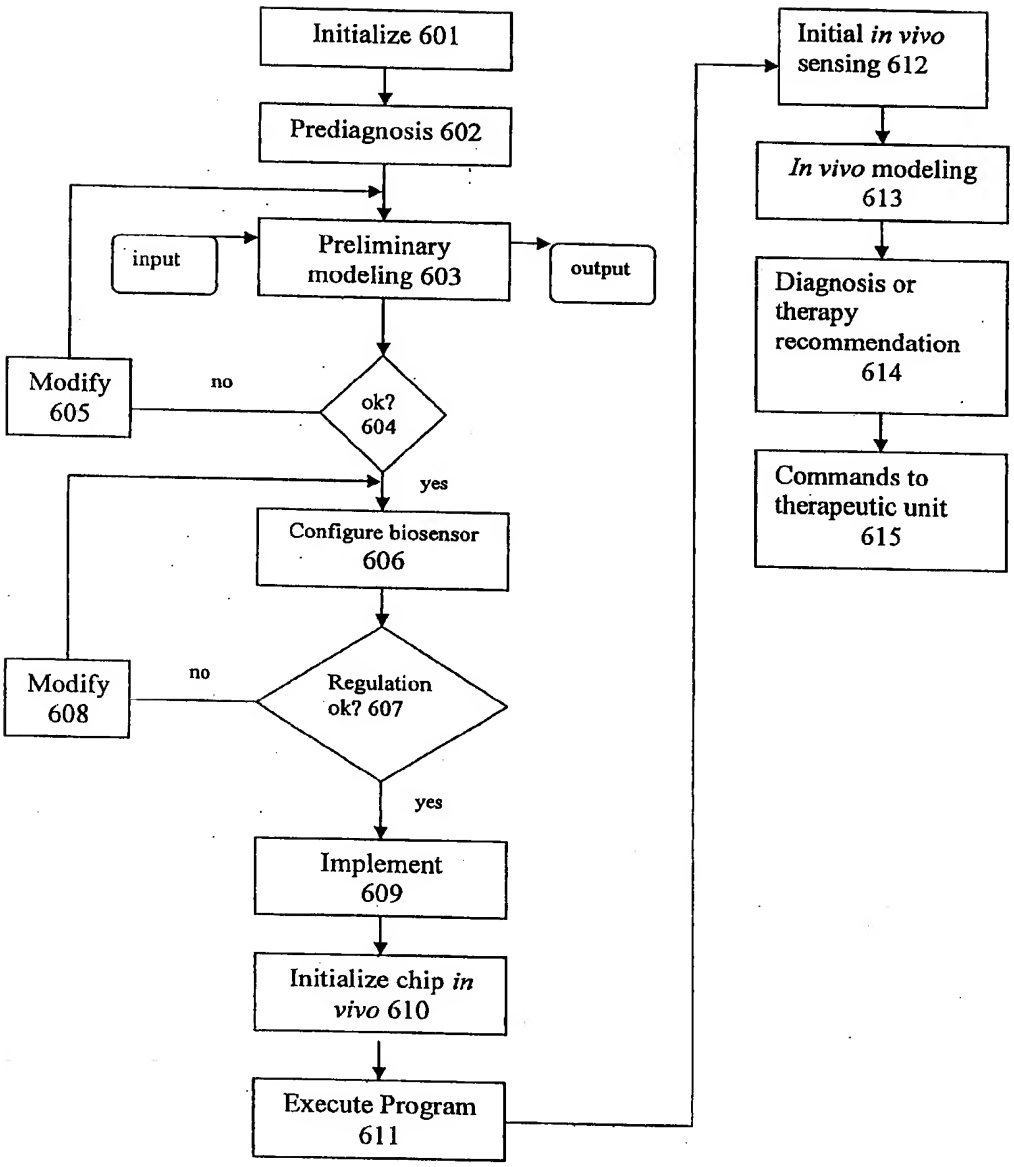

DNA unit 500
Input
DNA sensor 201
DNA therapeutic manufacture 501
DNA therapeutic reservoirs 502
DNA reconfigurable biosensor 503
Systems biology platform 104
Output

Figure 5


Initialize 601
Prediagnosis 602
input
Preliminary modeling 603
output
Modify 605
no
ok? 604
yes
Configure biosensor 606
Modify 608
no
Regulation ok? 607
yes
Implement 609
Initialize chip *in vivo* 610
Execute Program 611
Initial *in vivo* sensing 612
In vivo modeling 613
Diagnosis or therapy recommendation 614
Commands to therapeutic unit 615

Biosensor with Electronically Configurable Switching Array

The present invention relates to sensors for monitoring or analyzing biological hosts or material.

Reference is directed to GB 0722767.1 which is divided from the present application.

Various sensors are used to detect or measure macroscopic or molecular physiology in humans or other biological hosts. Additionally systems-biology software is available which provides computational modeling of molecular structures and interactions for genomics, proteomics, metabolomics, transcriptomics, computational chemistry, pharmcogenomics, or other purpose. Such tools, however, are not easily or automatically integrated or reconfigurable for interdisciplinary diagnosis or therapy.

The present invention provides a multi-functional electronically configurable switching array coupled programmably to a plurality of different sensors including a DNA sensor, an RNA sensor, a peptide or protein sensor, an antibody sensor, an antigen sensor, a tissue factor sensor, a vector and virus vector sensor, a lipid and fatty acid sensor, a steroid sensor, a neurotransmitter sensor, an inorganic iron and electrochemical sensor, a pH sensor, a free radical sensor, a carbohydrate sensor, a neural sensor, a chemical sensor, a small molecule sensor, an exon sensor, a metabolite sensor, an intermediates sensor, a chromosome sensor, or a cell sensor.

Preferably the sensor apparatus is configurable electronically to couple or interconnect selectively to one or more biosensor signals from said sensors.

Further preferred features are defined in the dependent claims.

In an embodiment, an integrated biosensor-simulation system combines one or more sensors to detect various conditions in biological target or host, and a software program or simulator using a system-biology model and sensor data adaptively to provide therapy, diagnosis, or other automated feedback. Preferably one or more sensors is reconfigurable by the simulator. Optionally food material for consumption by the biological target is sensed for application to the simulator, which may apply certain regulatory conditions. The simulator is coupled programmably to sensors.

Preferred embodiments of the invention are described below by way of example only with reference to Figures 1 to 6 of the accompanying drawings, wherein:

Figure 1a shows an implantable network biosensor including a biosensor platform in accordance with the present invention;

Figure 1b shows a sensor network incorporating the biosensor platform of Figure 1a;

Figure 2 shows the biosensor platform of Figures 1a and 1b;

Figure 3a shows diagrammatically systems-biology software utilised by the systems biology platform;

Figure 3b shows diagrammatically the arrangement of the systems biology platform, sensor network and a data storage and regulation overlay;

Figure 3c shows diagrammatically an arrangement of a system biology platform with a therapeutic unit and sensor unit;

Figure 4a shows diagrammatically an arrangement of a system biology platform, network and therapeutic unit;

Figure 4b shows diagrammatically a therapeutic manufacturing arrangement;

Figure 4c shows diagrammatically a therapeutic manufacturing arrangement with therapeutic reservoirs;

Figure 4d shows diagrammatically a sensor reconfiguration arrangement;

Figure 5 shows diagrammatically an arrangement of a DNA sensor unit and a systems biology platform, and

Figure 6 shows diagrammatically a diagnostic or therapeutic method.

Figure 1a is a diagram illustrating the architecture of an implantable network biosensor 100. It is contemplated

herein that sensor 100 may also operate without being implanted in a biological host, but instead through external contact or attachment thereto. Optionally multiple coupled sensors 100 may provide a fault-tolerant back-up or recovery facility, in case one or more sensors fails or malfunctions. Sensor 100 may be provided inside a host, e.g., mouth, larynx, blood vessel, vein, nose, ear, eye, heart, brain, lymph node, lung, breast, stomach, pancreas, kidney, colon, rectum, ovary, uterus, bladder, prostate, or other organ or using a portable mobile application externally, e.g. skin, fingernail.

Sensor 100 includes sensor unit 111, controller 112, therapeutic unit 113, and power module 114. Sensor 100 components may be interconnected or communicate with other components using electrical, electronic, or electromagnetic signals, e.g., optical, radio frequency, digital, analog or other signalling scheme. Power module 114 provides electrical energy for sensor 100 to operate.

Generally biosensor 100 may sense individual genome, proteome, metabolism, transcription, translation, blood pressure, carbohydrate and oxygen concentrations, or other factors as described herein. Data is provided by sensor 100 to integrated network 103 that applies systems-biology software 104 to verify, model, or analyze, for example, relative sequences, 3-dimensional structure, molecular interactions, or overall cellular and physiological environment.

Systems-biology software 104 processes information and determines treatment dynamically for individual real-time

physiological condition. Analysis report and other patient instructions are transmitted remotely as a telemedicine service to network 103, which provides tasks to components, such as pharmaceutical or biopharmaceutical reservoirs 109, reconfigurable biosensors 102, wireless telemetry system 106, therapeutic manufacturers 108, or other applications.

Sensors 102 may be hardware-reconfigurable or software-programmable according to user or systems-biology programming or report instructions. Ongoing or intermittent scheduled or random sensing events occurs between therapeutic components and pre-programmed and reconfigured micro/nano biosensors, along with proactive or reactive feedback to patient or user from systems-biology platform 104. Preferably the sensing process employs a micro or nanoscale sensor structure for minimal intrusion to individual health or physiology.

Optionally sensor system 100 provide wireless (RF) signal coupling with other sensors 100, such that communication occurs between different organisms having sensor 100. For example, sensor 100 may be implanted in a pregnant host and another sensor 100 may be implanted in the baby of such a host. Communication between sensors 100 may provide effective biological sensor signal transmission between separate hosts or organisms. Sensor 100 may be accessible according to the IEEE 1451 network interface format.

Another example for multi-host communication implements sensors 100 for communication between separate related individuals, such as potential sexual partners,

where one partner sensor 100 may sense a sexually transmitted disease (STD) in such a host, then such information is provided electronically to another host sensor 100 to produce proper antigens and antibodies to combat the STD.

Sensor unit 111 uses a positioning device or chip 101 to position, locate or immobilize effectively a target sample for analysis or sensing. The manipulated target sample comprises a biological molecule, organic or inorganic substance, such as cells, tissue, nutrients, chemicals, intracellular materials, extra-cellular materials, charged ions, pharmaceuticals, or molecular materials affecting host physiology.

Sensor unit 111 comprises a multifunctional biosensor platform 102 for sensing and monitoring multiple biological materials, concentrations, inorganic or organic materials, cellular material, genetic material, nucleic acids, proteins, amino acids, peptides, antibodies, antigens, fatty acids, lipids, steroids, neurotransmitters, inorganic ions, pH levels, free radicals, carbohydrates, chemicals, small molecules, cells, tissue, pharmaceuticals, toxins, metabolites, or physiological levels macroscopically, microscopically, or nanoscopically.

Controller 112 uses network 103 to couple components for signal or data communication. Network 103 communicates data electronically to systems-biology platform 104. Controller 112 may be implemented using personal, desktop, server, notebook, mainframe, wireless portable or other

computer or processing device having processor, digital memory and network or user interface.

Systems-biology platform 104 uses computer equipment, software programs or reconfigurable firmware or emulation logic devices to verify, model, simulate, or analyze stored or raw data using computational biology, such as bioinformatics, proteomics, metabolomics, pharmacogenomics or other analysis software or hardware tools. Systems-biology platform 104 interprets or integrates data from biosensor platform 102, and analyzes organism preferably as a whole on system level. Systems-biology platform 104 may be integrated within one or more integrated circuit, module or processor; or bilaterally communicate to outside non-host signal source through wireless communication unit 106.

Controller 112 may use data storage 105 for storing processed data or applications programs from systems-biology platform 104. Controller 112 includes wireless communication unit 106, allowing bilateral communication with an outside source, which may access or control sensor unit 111, controller 112, or therapeutic unit 113 through wireless communication unit 106.

Network 103 may couple therapeutic unit 113 with controller unit 112. Therapeutic unit 113 includes therapeutic manufacture 108 for providing pharmaceuticals, biopharmaceuticals, bio-catalytic chips or devices, tissue, or physiological treatments. Biopharmaceuticals include biological material for therapeutic use.

Therapeutic unit 113 includes therapeutic reservoir 109, which provides micro or nano-scale reservoirs containing pharmaceuticals or biopharmaceuticals. The contents of therapeutic reservoirs 109 may be provided or configured before sensor 100 is implanted in or attached to an organism, or may be manufactured and filled *in vivo* by therapeutic manufacture 108. Therapeutic reservoirs 109 may release or dispense contents when appropriately signalled by network 103.

Therapeutic unit 113 includes sensor manufacture unit 110, which may provide additional sensors *in vivo* for additional targeted sensing or monitoring. Sensors from sensor manufacture 110 are part of or comprise biosensor platform 102.

Figure 1b shows positioning chip 101 for immobilizing or positioning target or tissue samples on or in sensor 102 for bio-sensing as described herein. Positioning chip 101 may use micro-fabrication, micro-fluidics, or microbiology to manipulate, sort, or prepare samples, reagents, or other biological entities for analysis, high-throughput assays, or diagnostic applications. Positioning chip 101 may accomplish sample placement using a multi-channel patch clamp electrophysiology chip to control individual cells by applying current to cell ion channels, positioning cells onto a planar patch clamp, using for example, the Aviva Bioscience technique. The cell is sealed on-chip and analyzed or broken, and intracellular materials extracted and analyzed; if the cell is not analyzed, cellular material may be positioned for analysis by diffusion, or

other natural technique, or through micro-fluidic manipulation.

Optionally, positioning chip 101 comprises a microelectronic array or microfluidic assay, including electrodes or biosensors in which at least one microelectrode or sensor cavity or element is capable of generating controllable electric current or voltage for drawing probes, samples, or reagents to locations on sensor platform 102, allowing faster, controlled hybridization or analysis.

Positioning chip 101 may use micro or nano-chips with nanoscale channels or membranes, e.g., iMEDD NanoPORE membranes. Depending on the size of such membranes, pores selectively exclude antibodies or proteins, while allowing free exchange of glucose, nutrients, insulin, or other molecules. Positioning chip 101 may position mammalian cells of host organism, as well as bacterial, fungal, protozoan, or other unicellular or multi-cellular organisms for analysis.

Additionally positioning chip 101 may detect or collect micro-metastatic tumor cells circulating in the blood stream or other body fluids, including but not limited to nipple aspirate, cerebrospinal fluid, peritoneal wash, sputum or excrement such as urine and stool. Preferably enrichment of tumor cells from the bloodstream may occur in miniaturized or microelectromechanical (MEMs) version of the device such as autoMACS to collect circulating carcinoma cells from blood of patients with urologic cancers, or similarly using nanoparticles

conjugated with antibody to Epithelial Cell Adhesion Molecule to enrich for circulating tumor cells (CTC) of epithelial origin.

Further using positioning chip 101 in detection or collection, circulating prostate cancer cells in peripheral blood may be enriched, e.g., using the technique of OncoQuick in Greiner, Germany, by using anti-human epithelial antigen paramagnetic microbeads or enrichment for disseminated breast cancer cells using advanced density gradient centrifugation, circulating endothelial cells serving as a marker for vessel formation and vascular damage in cancer patients, such circulating cells being detectable for collection from peripheral blood using immunomagnetic beads coupled to antiCD146, an antibody raised against human umbilical vein endothelial cells.

Preferably collected tumor cells are analyzed on biosensor platform 102; for example, disseminated breast tumor cells may be analyzed by multiplex real-time RT-PCR (reverse transcriptase polymerase chain reaction) for mammoglobin, gabaII, B305D-C and B726P, or polymorphisms in carcinogen detoxifying UDP-glucuronosyl transferase UGT1A7 in the blood of patients with cancer of the proximal digestive tract. Also enriched, using anti-epithelial cells antibody Ber-EP4, e.g., Dynal Corporation technique, epithelial cells derived from the peripheral blood of prostate cancer patients can be analyzed using nested RT-PCR-PSA (reverse transcriptase polymerase chain reaction prostate specific antigen) assay as a sensor mechanism.

Biosensor platform 102 may employ twenty-five epithelial tumor cells in bone marrow and lymph nodes of esophageal carcinoma (pT1-3, pN0-1 and pM0) patients collected, using cytokeratin and EpCAM antibodies, respectively, by positioning chip 101 for micromanipulation in biosensor platform 102. Further DNA amplified by DNA sensor 201 using the Mse-adapter PCR method may be analyzed by comparative genomic hybridization (CGH) for DNA-gains, -losses and point mutations by single-strand conformation polymorphism (SSCP). Also total RNA isolated PBMC in peripheral blood of breast cancer patients, may be subject to RT-PCR luminometric hybridization assay for presence of human telomerase reverse transcriptase, which is highly expressed in the majority of tumor cells.

During the sensing operation, positioning chip 101 may place samples on biosensor platform 102 for analysis. Biosensor platform 102 measures, detects, sequences, and utilises other biological activities in serial or parallel in or out of the organism. Biosensor platform 102 may use a multi-functional high-throughput and density biochip having micro or nanoarrays, having substrates manufactured using glass, nylon, silicon, ceramic, metal, gel, membranes, synthesized nanomaterials, or other materials.

Biosensor platform 102 provides data gathered from sensor arrays to network 103, which provides data to systems-biology platform 104, where data is integrated or processed. Systems-biology platform 104 may analyze empirically-sensed and simulated factors of individual organism in combination, to determine or confirm the host profile of personal biological processes or makeup.

Systems-biology platform 104 may convey processed information to network 103. Network 103 communicates processed data to components coupled to network 103, including data storage 105, wireless communication unit 106, therapeutic manufacture 108, therapeutic reservoirs 109, or sensor manufacture 110.

Data storage 105 keeps records or stores processed data by systems-biology platform 104. Processed data from systems-biology platform 104, through network 103, optionally may be conveyed to wireless communication unit 106. Wireless communication unit 106 provides processed data access to an external source, such as a Global Positioning Satellite (GPS) receiver unit, media repository, personal computer (PC) or workstation, laptop, handheld computing device, cellular device, internal or external camera, another internal implantable or attached sensor or chip, external biological monitoring device, outside network, healthcare provider, pharmacist, insurance agent, or other device or service communicating with the bio-sensor.

Processed data from systems-biology platform 104, through network 103, may be conveyed to therapeutic manufacture 108, where therapies are manufactured according to host biological status or simulation output. The effectiveness or side-effects of the therapies, produced by therapeutic manufacture 108, are monitored by biosensor platform 102. Ongoing or intermittent feedback from biosensor platform 102, through network 103, to therapeutic manufacture 108 provides an automated or iterative therapeutic process.

Optionally therapeutic manufacture 108 stores biological therapies in therapeutic reservoirs 109. Therapeutic manufacture 108 or therapeutic reservoirs 109 communicate through network 103 for filling or dispensing. Processed data from systems-biology platform 104, through network 103, may be conveyed to therapeutic reservoirs 109, where respective therapies are released according to biological status. The effectiveness or side effects of therapies, released by therapeutic reservoirs 109, is monitored by biosensor platform 102. For example, biosensor platform 102 may sense therapeutic effectiveness or side effects, while systems-biology platform 104 analyzes negative or positive effects to make recommendations. Ongoing feedback from biosensor platform 102, through network 103, to therapeutic reservoirs 109 provides an automated or iterative therapeutic cycle.

Processed data from systems-biology platform 104, through network 103, optionally is conveyed to sensor manufacture 110. Sensor manufacture 110 comprises hardware or software-programmable (reconfigurable and software-programmable terms may be used interchangeably) biosensors *in vivo* that integrate into biosensor platform 102 for supplementary sensing. Sensor manufacture 110 may be used to monitor additional biological materials originally part of biosensor platform 102, as well as used functionally to replace damaged sensors. Sensor manufacture 110 may be used to sense newly-calculated operational conditions by systems-biology platform 104. Optionally sensor manufacture 110 may monitor interactions between novel drug therapies, produced by therapeutic manufacture 108, and the organism biology.

Appropriate timing of functions is preprogrammed before biosensor 100 is attached or implanted into organism. Time intervals for sensing are programmed according to external diagnosis, which can range from seconds, minutes, hours, weeks, or longer. Once initial sensing begins, the timing is adjusted based on processed information by systems-biology platform 104. For example if genetic mutations within genome are found to be rare within multiplying cells, systems-biology platform 104 instructs biosensor platform 102 not to monitor genome as frequently.

Conversely if the sensed or simulation parameter, input vector, stimulus, condition, environment or other host biological factor is changing frequently, or there is a high risk of change, then systems-biology platform 104 instructs biosensor platform 102 to increase the frequency of a particular sensor or assay. For example if the organism changes through an organ transplant, or is infected with new virus, systems-biology platform 104 instructs biosensor platform 102 to increase the monitoring frequency of antigen or antibody responses while decreasing such factors that are relatively stable.

Figure 2 shows biosensor platform 102 with a multifunctional array 200 coupled to a detection system 230, and an integrated sensor and detection system 231. Multifunctional array 200 serves as a programmable interconnect for coupling or switching various sensor devices, and interacts with samples. Detection system 230 interprets samples into data to be analyzed by systems-biology platform 104. Multifunctional array 200 may include

micro and nanoarrays (M/N arrays) and biochips to test or monitor biological functions in a particular organism.

Sensor components may include deoxyribonucleic acid (DNA) sensor 201, ribonucleic acid (RNA) sensor 202, peptide or protein sensor 203, antibody sensor 204, antigen sensor 205, tissue factor sensor 206, vector and virus vector sensor 207, lipid and fatty acid sensor 208, steroid sensor 209, neurotransmitter sensor 210, inorganic ion and electrochemical sensor 211, pH sensor 212, free radical sensor 213, carbohydrate sensor 214, neural sensor 215, chemical sensor 216, small molecule sensor 217, exon sensor 218, metabolite sensor 219, intermediates sensor 220, chromosome sensor 221, or cell sensor 222. The M/N arrays are arranged architecturally as a micro-electromechanical system (MEM) or as a nano-electromechanical system (NEMS). This miniaturized architecture, based on MEMS or NEMS devices, allows multiple M/N arrays in a condensed form.

DNA sensor 201 is used to detect the presence and/or sequence and/or structure of any DNA molecules including profiling for changes in methylation, monitoring gene expression, gene and DNA mapping, library screening, functional screen assays for nonsense and frame-shift mutations, scanning the whole genome including micro-array-based comparative genomic hybridization to measure and map DNA copy number aberrations, detecting disease markers, genotype single nucleotide polymorphisms (SNPs) including loss of heterozygosity analysis using SNP array hybridization and single-strand conformation polymorphism (SSCP), genotype organisms, examining protein-DNA interactions, and

determining genetic characteristics individual to the organism.

DNA sensor 201 utilizes high-throughput M/N arrays for hybridization and uses biochips, such as oligonucleotide M/N arrays, antibody M/N arrays, P1-based artificial chromosome (PAC) M/N arrays, bacterial artificial chromosome (BAC) M/N arrays, yeast artificial chromosome (YAC) M/N arrays, cosmid M/N arrays, cDNA M/N arrays, gene M/N arrays, whole-genome M/N arrays, SNP M/N arrays, gridded cDNA M/N arrays, Southern Blots, theme M/N arrays (array centered around a particular disease or gene family), bead M/N arrays (arrays made up of small beads containing capture oligonucleotides), bead based M/N arrays (arrays in which reactions take place on the surface of microbeads), gel-pad M/N arrays (arrays in which chemical and enzymatic reactions can be carried out on three dimensional pads, like miniature test tubes), microcantilever arrays (in which specific biomolecular interactions occur on one surface of a cantilever beam, such as changes in intermolecular interactions that generate sufficient surface stress to bend beam for optical detection), M/N gel electrophoresis chips and M/N arrays 2D gel electrophoresis chips, chromatographic protein M/N arrays, e.g., Ciphergen protein sensor, and hybridization techniques for deoxyribonucleic acid sensing. Phenotypic markers for DNA damage or repair include single-cell gel electrophoresis use the comet assay in which DNA damage is visualized, e.g., Komet 4.0 by (Kinetic Imaging Ltd) Imaging System.

Optionally for single nucleotide polymorphism (SNP) detection, DNA sensor 201 may utilise a so-called invader

platform, or other device for genetic sequencing of an individual. DNA sensor 201 can analyze peritoneal fluid from patients with ovarian cancer for loss of heterozygosity (LOH) at chromosomal arms 13 q(BRCA2 locus), 17 (BRCA1 and p53 loci) and 22q and for mutations in their p53 and k-ras genes. It can detect SNP (936 C>T) in 3' UTR of vascular endothelial growth factor gene (VEGF) in DNA extracted from blood of patients with breast cancer.

Further DNA sensor 201 can identify polymorphisms in carcinogen detoxifying UDP-glucuronosyl transferase UGT1A7 in the blood of patients with cancer of the proximal digestive tract. Also methylation abnormalities in the promoter CpG islands of p16, HOX A9, MAGE A1 and MAGE B2 can be detected in the sputum of lung cancer patients with DNA sensor 201. Sharply-elevated levels of stool DNA can be detected by DNA sensor 201 in patients with colorectal cancer. Stool DNA of surface epithelial cells is quantified using Picogreen fluorimetry.

DNA sensor 201 can detect chromosomal aneuploidy in cervical intraepithelial neoplasia or dysplasia using an interphase cytogenetic technique known as dual-color fluorescence in situ hybridization (FISH) targeting chromosomes 1, 7, 9 and 17 in Pap-smear slides and a thin layer of cervical cells.

Using DNA sensor 201, nipple aspirate fluid (NAF) containing epithelial cells shed from the breast ductal system can be analyzed. Extracted NAF DNA can be PCR amplified and analyzed for loss of heterozygosity in nuclear

genome and deletions in mitochondrial genome using microsatelite markers and primer pairs, respectively.

Further DNA sensor 201 can be used to detect acute lymphoblastic leukaemia prenatally by analysing fetus blood to detect TEL-AML1 by FISH and genomic breakpoints by long-distance PCR. Using DNA sensor 201 and genomic DNA from whole blood, germ line polymorphism in KLK10 at codon 50 (GCC to TCC) associated with risk of occurrence in prostate cancer can be detected.

Also using DNA sensor 201, epigenetic changes, such as changes in GSTP1 methylation associated with prostate cancer can be detected in bodily fluids, e.g., urine and plasma, of prostate cancer patients. This detection uses real-time quantitative MSP and conventional MSP.

Further DNA sensor 201 is used to search for pieces of DNA in blood that are abnormally long, which is a signature of dying cancer cells; this test can be used for early diagnosis for patients with gynaecologic and breast cancers. Optionally oligonucleotide array-based genotyping platform, such as Perlegen, is used for accelerated SNP analysis, allowing whole-genome scanning by DNA sensor 201.

RNA sensor 202 may be used to detect the presence, sequence or structure of RNA molecules, such as spliced and un-spliced RNA, mRNA, tRNA, rRNA, improperly transcribed RNA, properly transcribed RNA from diseased DNA sources, ribozymes, RNAi mechanism and application in relation to cancer therapy, or changes or differences in mRNA levels, or structures made of ribonucleic acids. RNA sensor 202 utilizes

high-throughput M/N arrays for hybridization techniques, inclusive of DNA sensor 201. Probes may be made to hybridize with RNA molecules, and Northern blot may be used in place of Southern blot technique.

RNA from enriched epithelial cells using anti-epithelial cells antibody Ber-EP4, e.g., per technique by Dynal Corporation, derived from peripheral blood of prostate cancer patients is analyzed for using nested RT-PCR-PSA assay by RNA sensor 202. Further, RNA sensor 202 can be used instead of second-look laparotomy in women with ovarian carcinoma treated with surgery and chemotherapy who show no sign of disease. Processed peritoneal washings are analyzed by a telomerase repeat amplification protocol (TRAP) assay to detect residual disease. Total RNA isolated PBMC in peripheral blood of breast cancer patients is subjected to a RT-PCR luminometric hybridization assay for presence of human telomerase reverse transcriptase that is highly expressed in majority of tumor cells.

Peptide or protein sensor 203 is used to detect primary, secondary, tertiary, or quaternary structures or activity of amino acid-based structures, such as sequence, enzymatic activity, protein function, interactions with agonists and antagonists, interactions with organic or inorganic structures or molecules, interactions with membranes, folding and enzymatic changes resulting from external factors, such as temperature, pH, ion concentrations, etc., N or C terminal characteristics, prions and misfolded proteins, amount and concentrations of proteins, bound and unbound state of proteins, sub-cellular localization, phosphorylated and dephosphorylated states, stages of degradation by proteases,

stages of translation, gene and protein expression levels, e.g., using techniques such as ANTIBIOMIX (Milagen, Inc.) or Antigen Retrieval (Biogenex Laboratories, Inc.), protein-protein interactions, protein-small molecule interactions, protein-antibody interactions, protein mutations due to transcription and translation mistakes, or measurable factors associated with amino acid based structures. Sensor 203 may be implemented using electrophoresis tag or microassay to identify protein or gene simultaneously, e.g., by Aclara eTag assay (Mountain View, CA).

Peptide or protein sensor 203 utilizes high-throughput M/N arrays for hybridization and use biochips, such as protein M/N arrays, proteome M/N arrays, whole-proteome M/N arrays, electrospray fabricated protein M/N arrays, gene expression M/N arrays, reverse transfection M/N arrays (for example membrane proteins that are difficult to purify), functional protein M/N arrays, Western blotting, microcantilever arrays, or quantitative and qualitative high-throughput techniques for amino acid entities.

Peptide or protein sensor 203 can be used to detect proteins in cerebrospinal fluid of patients with primary brain tumors. Differentially-expressed proteins in processed CSF are digested and peptides identified by mass spectrometry. The presence of tumor-related proteins such as VEGF and VAV signifies presence of a primary brain tumor (179). Sensor 203, like SELDI protein-chip, similarly may be used to identify sixteen protein biomarkers in urine of bladder cancer patients, or instead of second look laprotomy in women with ovarian carcinoma who have been treated with surgery and chemotherapy and show no signs of disease.

Processed peritoneal washings may be analyzed for telomerase activity to detect for residual disease.

Protein or peptide sensor 203 may be used in detection of diminished levels of N-CAM of <130 kDa in human serum of patients with brain tumors and the 80 kDa form associated with glioma. Further, protein and peptide sensor can be used in diagnosis of breast cancer by analysis of nipple aspirate fluid (NAF). Using SELDI-TOF capability, the presence of peptides at 4233.0 Da and 9470.0 Da is associated with cancer and the presence of 3415.6 Da and 4149.7 Da may be expected for normal samples. Thus sensor 203 can differentiate between diseased and unaffected populations.

Similarly protein sensor 203 may be used in breast-cancer diagnosis by analysis of serum samples. Samples applied to metal affinity capture chips activated with Ni^{2+}. Using SELDI protein chips/ mass spectrometry feature and software to detect selected discriminatory peaks separate cancer from non-cancer groups.

Using the same features of sensor 203, serum is analyzed to differentiate between hepatocellular carcinoma (HCC) and chronic liver disease (CLD), where α-fetoprotein fails as a biomarker. By detecting potential biomarkers in this way, the system can provide a diagnosis method for HCC. By using protein sensor 203 in the diagnosis of prostate cancer, protein of 50.8kDa can be detected in serum even where PSA levels are <4ng/mL.

Further protein sensor 203 may be used in diagnosis of colorectal cancer detecting elevated HER-2 levels using

standard ELISA and immuno-histo-chemistry (IHC) techniques. Elevated levels of secreted urokinase-type plasminogen activator (uPA) can be detected by sensor 203 in serum for diagnosis of pancreatic cancer using sandwich ELISA or similarly, elevated levels of kallikrein 10 in serum for diagnosis of ovarian cancer, or elevated levels of basic fibroblast growth factor (bFGF) in nipple aspirate fluid in diagnosis of breast cancer, or elevated levels of fibroblast growth factor-2 and pleiotropin in serum for testicular cancer diagnosis or interleukin 6 in the serum of hormone-refractory breast cancer patients using immunoassay techniques.

Antibody sensor 204 may be used to detect monoclonal or polyclonal antibodies. Similarly to the above sensors, hybridization with M/N arrays may be used. Probes may be chemical or molecular biological material that hybridize to the targeted antibody, such as DNA, RNA, or a peptide, protein, small molecule, steroid, or lipid. Microcantilever arrays and other binding techniques can be applied.

Antibody sensor 204 may use so-called phagotope biochip to display phage with epitopes that react with antibodies in sera of patients with ovarian cancer, or other cancers. Also the presence of elevated levels of anti-survivine autoantibody in serum of head or neck cancer patients is detected by antibody sensor 204 using recombinant protein survivine as antigen.

Antigen sensor 205 may be used to detect or recognize individual immune response factors. For example antigen sensing may detect autoimmune response factors, such as

sensing multiplex character autoantibody response in systemic lupus erythematosus, rheumatoid arthritis, or multiple sclerosis. Another example of antigen sensor 205 application may be identification or targeting of cell surface antigens for cancer therapy, e.g., the Genentech approach.

Antigen sensor 205 may be used for early diagnosis of lung cancer for determining the efficacy of chemotherapy by detecting nucleosomes in serum using assay, e.g., Cell Death Detection ELISAplus (Roche Diagnostics). Further antigen sensor 205 may detect tumor-associated antigens such as CYFRA21-1 for non-small cell lung cancer, and CEA, NSE and ProGRP for small-cell lung cancer.

Other sensing techniques for cancer detection contemplated herein include the anti-malignin antibody screen test and tests for cancer markers including alpha fetoprotein (AFP), CA 15.3, CA 19.9, CA125, carcinoembryonic antigen (CEA), EVP test for Epstein bar virus, T/Tn Antigen test, TK-1 test and prostate specific antigen (PSA) or free PSA (fPSA) test. For bladder-cancer bladder-tumor-associated antigen test (BTA), BTA stat test, BTA TRAK test, fibrin/fibrinogen degradation products test (FDP), and NMP22 assay. Protein-based markers may illuminate and map abnormal cells, e.g., Inpath system. Other blood tests include the CBC blood test, biological terrain assessment (BTA), Pre-Gen 26, and the telomerase test or DR-70 test.

Tissue-factor sensor 206 may use a tissue factor M/N array to sense tissues, tissue factors, or tissue origin, using probes or antibodies to hybridize with targets. Tissue-factor sensor 206 may detect an increase in prostaglandin E_2

production in cells that over-express COX2. This detection is associated with enhanced growth, migration and invasion as in bladder tumors.

Lipid or fatty acid sensor 208 may provide membrane mapping, M/N gel electrophoresis chips and M/N arrays 2D gel electrophoresis chips, detergent analysis, M/N array analysis of glycolipids and membrane proteins, membrane fluidity analysis, cholesterol analysis, or other tests to examine cellular or intracellular organelles lipid bilayers.

Lipid or fatty acid sensor 208 may detect changes in an exposed membrane; for example, such sensor 208 may produce an antibody, with a traceable label conjugated thereto, to anionic phospholipids (AP), such as phosphatidylserine, phosphatidylinositol and phosphatidic acid, that are more specific for AP than annexin V. When released into the blood stream this antibody binds endothelial cells activated by inflammatory cytokines, hypoxia, hydrogen peroxide, thrombin or acidic conditions, and thus, tumor blood vessels having increased exposure of anionic phospholipids on their surface. Localization of the label enables localization of the tumor.

Lipid or fatty acid sensor 208 may detect levels of accumulation of synthetic membrane-permeable alkyl-lysophospholipids (ALPs), such as Edelfosine, Mitelfosine and Perifosine, that are anticancer agents that interfere with lipid mediated signal transduction.

Vector or virus vector sensor 207 may use a microarray or assay with a known sequenced virus attached e.g., from DeRisi Laboratory. Unknown viruses may be detected through

examining homology to known viruses, and subsequent arrays can be manufactured by sensor manufacture 110 to detect new viruses. Optionally assays that detect homologs can be applied, such as the Celera Diagnostic ViroseqTM HIV system for detection of mutations in human immunodeficiency virus (HIV) genome that confer drug resistance. Optionally assays for virus RNA can be used, such as the Bayer Diagnostic Versant® HIV-I RNA 3.0 Assay for qualification of HIV-I RNA in plasma of infected people.

A further microparticle enzyme immunoassay (AxSYM HbsAg V2), e.g., from Abbott Laboratories, may be used in quantifying reactivation of HBV during chemotherapy for lymphoma with Doxo rubicin along with real-time quantitative PCR specific to region of major S protein. Virus and virus vector sensor 207 may be used for detection of oncolytic virus replication in tumor tissues.

Steroid sensor 209 detects levels of steroids in the body, and monitors or controls levels of steroid hormones. Sensor 209 targets hormonal changes associated with puberty, menopause as well as those arising in fitness-conscious steroid-pumping athletic individuals.

Neurotransmitter sensor 210, small molecular sensor 217, or exons sensor 218 detects using M/N arrays, such specific antibodies as probes that hybridize with desired targets. Inorganic ion or electrochemical sensor 211 may detect ionic concentrations using various techniques, using MEMS technologies with dielectric currents, microfluidics, or dialysis on a N/M platform. pH sensor 212 may read pH by detecting H_3O^+ concentrations using silicon oxide pH sensors,

e.g., from Intelligent Pill. Free radical sensor 213 may be used to measure free radical activity, by using antioxidants as probes.

Carbohydrate sensor 214 may use oligosaccharide arrays, polysaccharide arrays, or carbohydrate chips, e.g., the Glycominds glycochip, to measure glycan-protein interactions such as those involving enzymes, antibodies, and lectins. Branched carbohydrates may bind to lectins involved in cell adhesion and migration processes. Also, a naturally branched carbohydrate such as Lewis y, which is over-expressed in, for example, colon and ovarian cancer, may be detected by carbohydrate sensor 214. Such sensor 214 may utilise a whole blood glucose (WBG) monitoring system, or a continuous glucose monitor, e.g., from Sensors for Medicine Science.

Neural sensor 215 measures action potentials or voltage between neurons in the central nervous systems, using thin-film M/N electrodes as front-end sensors in MEMS and NEMS.

Chemical sensor 216 senses native or foreign chemicals, such as toxins, pharmaceuticals, vitamins, minerals, or other organic or inorganic chemicals. Chemical M/N arrays may be used, in which arrays of small organic compounds may be used to analyze interactions of proteins with various compounds. Conversely proteins or RNA may be used as probes to detect chemical substances.

Chemical sensor 216 may measure e.g., levels of the carcinogen benzo(*a*)pyrene diol epoxide, a metabolic product of benzo(*a*)pyrene found in tobacco smoke, known to cause 9p21

abberations in peripheral blood lymphocytes in bladder cancer cases. Further chemical sensor 216 may measure the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) that can induce transformation of human breast epithelial cells, and may be directly related to initiation of human breast cancer in smokers.

Metabolites sensor 219 uses protein or antibody M/N arrays that hybridize to particular metabolites. Sensor 219 is useful to detect excessive build up of metabolites. For example metabolites sensor 219 can measure serum homocysteine levels, associated with increased risk of cervical cancer, and further DNA sensor 201 may detect common polymorphisms in one-carbon metabolic pathway; examples of such mutations include MTHFR C677T, MTHFR A1298C and MTR A2756G. Increasing copies of MTHFR 677 variant polymorphism are associated with increased homocysteine levels whereas increasing copies of MTR 2756 variant polymorphism are associated with decreased levels of such metabolite.

Intermediates sensor 220 uses various protein and antibody M/N arrays that hybridize to particular intermediates. Sensor 220 is useful to detect excessive build up of intermediates; also sensing a specific sequence, or the tertiary or quaternary structure of intermediates is used in drug design specificity.

Chromosome sensor 221 senses abnormalities in chromosome folding, such as faulty histones, senescence-associated heterochromatic foci, or SAHF, since genes contained in these chromosomal regions are switched-on in proliferating cells,

but are switched-off or "silenced" during cellular senescence.

Cell sensor 222 attaches whole living cells as probes, and is used for interactions with whole cells, such as cytotoxicity, drug metabolism, pharmacokinetics, target validation, interactions with other cells, extracellular materials, phenotypic analysis of genes and interfering RNA, as well as other biomolecules and compounds, using e.g., the Excellin Life Science bionic chip, which provides cell growth on chip. Effectively the cell becomes part of the chip, which allows manipulation and analysis of cell using microelectronics; the chip sends electrical signals through an on-board living cell, which detects changes in cell-membrane structure. The bionic chip can monitor and detect conditions that can cause cellular damage.

Optionally image cytometric measurement of breast fine needle aspirates can be used in cell sensing to predict nodal involvement in breast cancer, utilising DNA ploidy, S-phase fraction, G0G1/G2M ratio, and minimum (start) and maximum (end) nuclear pleomorphism indices (NPI). Further cytometric imaging allows differentiation between normal cells in which PML protein resides in discrete PML bodies and promyelocytic leukemic cells in which PML protein is genetically rearranged or dispersed throughout the nucleus.

Sensor unit 111 may measure or transmit blood pressure, flow rate or other sensor data wirelessly to controller unit 112, similarly to the so-called cardioMEMS devices for monitoring pressure within an aortic aneurysm. Biosensor 100 is implanted using a catheter and transmits data to

controller unit 112. Optionally such a device can be used assessing circulation to organ after transplant or reconstructive surgery. This provides the physician with an early indication of whether surgery is successful and prevents irreversible damage to organ.

Biosensor 100 may use an implantable blood-flow monitoring system for providing synchronized blood vessel flow or myocardial wall contractility data to an external monitor independently of transcutaneous leads. Further, since heart failure (HF) status of a patient is determined based on the morphology of a signal representative of arterial pulse pressure, the signal can be a plethysmography signal that is produced by an implantable or non-implanted sensor.

A time-derivative sensed signal may be produced based on a signal representative of arterial pulse pressure.

The time derivation signal can be used to determine maximum and minimum peaks of a signal representative of arterial pulse pressure. HF status can be accessed directly from the time-derivative signal.

Biosensor 100 can be implanted using a placement catheter, an endoscope, or a laparoscope; such device can be secured in LV or heart wall, e.g., using a corkscrew, helical anchor, harpoon, threaded member, hook, barb, fastener, suture, or mesh or coating for receiving fibrous tissue growth.

Biosensor 100 provides a less-invasive chronic measurement of left ventricular blood pressure or other

parameters. Biosensor 100 can perform a cardiosaver function to indicate to a human subject that a myocardial infarction is occurring; data is transmitted wirelessly to controller unit 112 for systems-biology analysis. Therapeutic reservoir 109 can inject a thrombolytic or anti-thrombogenic agent into the bloodstream promptly to dissolve the thrombus that caused the myocardial infarction, and prevent formation of additional thrombi.

Biosensor 100 may sense impedance measurements of the heart, or respiratory or patient motion, and from these measurements, generate an alarm signal when measurements indicate occurrence of a cardiac arrhythmia. Optionally a rate-responsive pacing system includes a sensor of minimum oxygen content in the right atrium over a prescribed time interval, and uses such minimum oxygen content as a control parameter for adjusting the rate of a pacemaker.

Optionally for sensors in multi-functional array 200, nano-particles that specifically binds to particular molecules can be used to detect a sequence, or folding or binding interactions, function, or overall characteristics. Once bound to particular biological molecules, the distances between nanoparticles result in different observable properties, such as color or pattern.

Array 200 may be configured electronically by systems biology platform 104 to couple or interconnect selectively according to simulation or modelling to access the actual host condition via one or more biosensor signals. Such sensed signal set may be compared by the simulator against a model or other software prediction to confirm the health of the

host or target material or detect problems, as described herein.

Nanoparticle arrangements on biological molecules provide or indicate function, e.g., as in the Northwestern University DNA-Driven Assembly of Biomaterials system. By attaching gold particles to DNA nucleotides, DNA hybridizes with complementary strand and creates specific arrangement of gold particles. That arrangement of nanoparticles gives a detectable color or pattern, which can be detected by an optical device, and DNA can be sequenced.

Measuring color differences between nano-particle arrangements can also be applied to other biological molecules, e.g., as in the Northwestern University Nanoscale Bioassay for Specific Antibodies. Rather than engineering nanoparticles that attach directly to the biological molecule, nanoparticles can be attached to specific antibodies. Binding of antibodies to targeted protein, DNA sequence, small particle, lipid, chemical, or other biological produces a particular color that is detectable or analyzable.

Also Nanoplex Technologies Nanobarcode Particles, made of different metals attached to biological molecules for multiplexing bioassays use probes attached to alternating metals on a Nanobarcode to hybridize with biological molecules; then current can be run through the Nanobarcode to determine molecules that bind to probes.

Detection system 230 may produce data from hybridization M/N arrays and other analysis systems e.g., fluorescent

scanners, laser scanning phosphorimagers, mass spectrometry, fiber optics, atomic force microscopy, parallel surface plasmon resonance imaging (allowing direct analysis of binding events without the need of reporter systems or tags), conclusive-induced dissociation (CID) mass spectra through electrospray ionization tandem mass spectrometry (ESI-MS) on triple or quadruple or ion trap mass spectrometers, real-time polymerase chain reaction (PCR), PCR, Fluoresecence *in situ* Hybridization (FISH), or charged coupled devices (CCDs).

Integrated sensor or detection system 231 may produce data from samples, without separating detection from hybridization or using other techniques. Optionally a semiconductor-based M/N array can be used, e.g., the CombiMatrix matriXarray; such an array allows precise, digital control of electrochemical detritylation, and may include an embedded sensor formed in a semiconductor substrate, as an alternative to conventional fluorescence technology. Hybridization with the array sends direct electronic signals for analysis.

Another example of the integrated sensor or detection system 231 can be the GeneFluidics 3D micro-fabricated platform with embedded electrochemical sensor array. This platform conducts molecular analysis of raw DNA or protein samples, e.g., no PCR or immunoassays. Electrochemical detection of samples, such as whole blood, saliva, stomach acids, or other bodily fluids, uses current to measure electron transfer with a current signal associated with hybridized nanomolecules, e.g., ssDNA, or hybridisable nanoparticles.

Biosensor 100 generally comprises a biological microelectromechanical (bio-MEMs) sensor chip or detection or transducer device that may be implemented or computer-modeled for operation in silicon, silica, glass, polymer or other substrate or in an instrumentation cavity, beam, surface, or channel, or in encapsulated molecules, a membrane, a quantum dot or nanocrystal (e.g., CdS, CdSe, CdTe, ZnSe, or other colloidal group II-VI semiconductor), matrix or array for single or multi-channel independent signal detection in two or three dimensions in vitro or in vivo.

For example, sensor 100 may serve as high-throughput and sensitivity bio-physical, pharmaceutical or chemical recognition probe or cartridge for identification and/or characterization of host tissue or serum DNA, RNA, nucleic acids, protein, lipids, carbohydrates, enzymes, aptamers or other biomolecular or signal reporter targets or for any interaction, mutation, mass or rate thereof. Also such sensor may provide integrated, monolithic, discrete, or distributed, reagent-based or reagentless, microfluidic lab-on-chip microbiology mass spectrometry, flow immunosensor (e.g., FAST monitor for food or water quality), microarray or microassay functions, such as growing viruses, bacteria or other eukaryotic or prokaryotic cells in microcells, nucleotide hybridization, polymerase chain reaction, molecular imprinting, chemical synthesis, ligand fishing, phage selection and concentration, multicomplex formation, diffusion limited concentration, or challenging antibiotics for rapid target detection, antibody susceptibility determination, or affinity and kinetic analysis.

Biosensor 100 may be implemented in a quartz crystal microbalance for detecting or monitoring a physical or chemical associated mass change or dissipation rate. Also a whole cell or host sensor detection method may sense radioisotopes, fluorescence, or colorimetric or electrochemical indications, or chemiluminescence, or bioluminescence. Additionally a molecular or lipid-layer membrane-based sensor e.g., an Ion Channel Switch biosensor using alternating current or voltage may operate to report ionic changes.

Furthermore encapsulated molecules may be employed in probes utilising biologically localized embedding (e.g., PEBBLE nanosensors for intracellular chemical sensing, which may be delivered via gene gun, picoinjection, liposomal delivery, or phagocytosis, use matrices of cross-linked polyacrylamide, cross-linked decyl methacrylate, and sol-gel silica) for H^+, Ca^{2+}, K^+, Na^+, MG^{2+}, ZN^{2+}, Cl^-, NO_2^-, O_2, NO and glucose detection; optionally an encapsulated outer shell may be modified as a configurable platform to target selectively specific biological locations or antibodies, such as including or excluding species variously reactive to passing through or filtered by the polymer membrane.

Biosensor 100 may recognize a protein for antigen-antibody recognition, particularly by localizing or mapping protein residue epitopes. For example a sensor contacting at the epitope-paratope interface can function via crystallographic analysis of one or more poly- or monoclonal or antigen-antibody complexes. Also sensor 100 may detect cross-reactive binding with antiprotein antibodies using synthetic peptides as antigenic binding probes for free

peptides or peptides adsorbed on the solid-phase, or conjugated to a carrier or attached to a synthesis support.

Additionally sensor 100 may detect a decrease in cross-reactive binding to identify critical residues in peptides via systematic residue replacement, as well as other protein-protein interaction, for example, between protease-inhibitor, antibody-antigen, enzyme-inhibitor, hormone-receptor, or signal transduction or transcriptional complexes. The protein sensing analyte may include fatty acids, maltose, biotin, Ca^{2+}, Co^{2+}, Zn^{2+}, Cu^{2+}, glucose, glutamine, or other organic serum or tissue material.

Biosensor 100 may immobilize or control the orientation of the biomolecular target binding or catalytic sites via adsorption, entrapment behind a membrane or in a polymer or sol gel, covalent coupling, surface-immobilized polymer, or other capture system. Sensor orientation control may be accomplished via covalent coupling with attached glycosides, generation of specifically-located thiol groups, use of antibody-binding proteins, avidin/streptavidin capture system, or use of tags with engineered antibody fragments.

Additionally sensor spatial control of surface immobilization may use soft lithography for substrate or surface patterning to introduce surface function, deposition control by physical placement, light-directed immobilization and patterning, or electro-chemical deposition control, for example, using elastometric polymer poly dimethysiloxane PDMS.

Also a molecular imprinting polymer sensor may employ an affinity sensor where a response is produced by accumulation of a template on the sensor surface, a receptor sensor where a response is generated by a change in polymer characteristic or induced by template interaction, or an enzyme-mimicking sensor where a response is generated according to a change in environment induced by molecular imprinting polymer-mediated catalytic reaction.

Furthermore an antibody-based sol-gel sensor may use competitive assay detection, where the antibody is encapsulated in gel, the sol-gel sensor is immersed in a sample containing known fluorescently labeled analyte solution, excess analyte is washed from the gel, and fluorescence emission from the remaining bound analyte is measured optically; displacement assay detection, where the antibody is encapsulated in gel with pre-bound fluorescently-labeled analyte, and gel is removed from solution and fluorescence emission from undisplaced analyte is measured; and fluorescence quenching detection, where the fluorescently labelled antibody is encapsulated in gel, which is immersed in sample, and bound analyte quenches fluorescence from an antibody tag.

Biosensor 100 may employ an optical biosensor or transducer with various assay formats. A direct assay may not use any label, and analyte surface binding is measured directly. A sandwich assay secondary antibody binds to surface-bound analyte molecules after analyte binding to a sensor surface. A competitive assay enables binding-site competition on the sensor surface, and a low sensor signal is obtained for high analyte concentration.

The optical transducer sensor may use an input grating coupler (e.g., a bidiffractive grating coupler), a prism coupler, a planar or nonplanar, polarimetric, ion-exchange or deposited-rib, channelized or non-channelized waveguide or interferometer (e.g., A Mach-Zehnder interferometer), as well as a surface plasmon resonance sensor (e.g., the BIACORE system) using a prism coupler, a resonant mirror with a vibro-stirrer (e.g., Iasys), an evanescent wave fiber optic biosensor for multi-analyte detection (e.g., RAPTOR antibody identification system), a displacement flow detector, or other optical or time-resolved or phase fluorescence transducer (e.g., to detect fluorophore-labeled binding protein or fluorescence resonance energy transfer), or fiber optic elements.

Biosensor 100 may employ an acoustic transducer or wave device, such as a bulk or surface acoustic wave device, a thickness-shear mode resonator, a shear-horizontal surface acoustic wave, acoustic plate mode, or love wave sensor, for example, to detect and characterize sensitive biological binding events in real time without labelling, by measuring energy loss occurring at a liquid-solid biomolecular interface.

Biosensor 100 may employ fast-flow injection or microtiterplate immunoassay using enzymatic amplification electrodes, for example, via bi-enzymatic substrate recycling for signal amplification using an electrochemical or bioelectrocatalytic redoxlabel immunoassay. A bioelectrocatalytic sensor electrode material for detecting phenolic targets via alkaline phosphatase measurement, for

example, may include glassy carbon, graphite, carbon paste or ink, or gold.

Preferably sensing devices or techniques are provided or performed in miniaturized implantable format. However some sensor devices or methods may require a sample from an implanted device to be transferred to an instrument located outside the body. Data generated by such an instrument is transmitted to systems-biology platform 104 for analysis or modeling.

Biosensor platform 102 sensors, detection systems, or components may be applied to parasitic or symbiotic organisms, such as bacteria, fungi, protozoa, plants, or other unicellular or multi-cellular organisms provided in a host organism, for example DNA sensor 201 may sense the DNA structure of a fungus cell living within such organism, peptide or protein sensor 202 may read its protein structures, and other sensors may read other biological properties. This information along with data from the host organism is interpreted with systems-biology platform 104, and a solution to expunge fungi is calculated or implemented.

Figure 3a shows software components of systems-biology platform 104. Once biosensor platform 102 produces comprehensive data on the system, it is sent to network 103 and processed or analyzed by systems-biology platform 104.

Systems-biology platform 104 analyzes the overall or partial structure of the system or host, combining data from sensor components as well as model data of biosensor platform 102. Systems-biology platform 104 uses software for analyzing

genomics 301, proteomics 302, computational chemistry 303, pharmacogenomics 304, computational biology 305, computational biophysics 306, computational cell behaviour 307, pharmacokinetics 308, metabolomics 309, transcriptomics 310, bioinformatics 311, other computational behaviour of the biological system, or other "omics" studies.

Other software may be integrated to understand or implement a biological system on a personalized level, e.g., specific gene sequence, individual protein interactions, personal localized mRNA levels, dynamics of a particular system, methods of control, personal cytotoxicity, and methods to design and modify the system; comprehensive data set is generated to understand fully or partially the subject organism.

A genomics unit 301 may map, sequence, analyze, or discover the function of an organism genome. Structural or functional genomics may be used in genomics 301. A proteomics unit 302 analyzes an organism proteome, describing a set of proteins expressed during the lifetime of a cell or group of cells. A proteomics unit 302 performs structure determination, at a lower level, to perform functional analysis, or cell modeling at higher level of modeling.

A computational chemistry unit 303 uses algorithmic tools to facilitate chemical analyses. Chemical analysis occurs at atomic or molecular level, examining how individual and groups of atoms, compounds, or other structures interact with a living system; further it analyzes chemical relationships between biological structures.

A pharmacogenomics unit 304 calculates potential drug responses based on personalized genetic information. This information is useful for determining appropriate therapies or preventing adverse reactions.

A computational biology unit 305 uses algorithmic tools to facilitate biological analyses. A computational biophysics unit 306 uses algorithmic tools to facilitate biophysical or biokinetic analyses. A computational cell behaviour unit 307 uses algorithmic tools to facilitate complete analyses of intracellular or intercellular behaviour.

A pharmacokinetics unit 308 determines or predicts kinetic interactions between potential drugs and organism biological molecules, taking into account variable interaction factors, such as sterics, charge, dipole forces, or other factors that determine molecular interactions.

A metabolomics unit 309 analyzes the organism's overall metabolic profile, such as metabolism rates, amounts of metabolite intermediates, metabolic efficiency, structure of metabolic proteins, interactions between metabolic proteins and therapies, phosphorylative rates, or other aspects of individual metabolism.

A transcriptomics unit 310 analyzes the organism's transcription profile, such as efficiency, transcription errors to mRNA, intron-exon-splicing, biological transcription machinery, or other attributes of organism transcription.

A bioinformatics unit 311 undergoes database-management activities, involving persistent sets of data that are maintained in a consistent state over indefinite periods of time. Bioinformatics unit 311 provides information content or flow in biological systems and processes; it serves as bridge between observations (i.e., data) in diverse biologically-related disciplines and derivations of understanding (i.e. information) about how systems or processes function, or subsequently the application.

Figure 3b shows the flow of information between systems-biology platform 104 and data storage 105 through network 103. This allows comparative studies between previously programmed and stored data with real-time computation; comparative studies serve as check against errors made by biosensor platform 102 and provide insights into overall systems understanding.

Also data storage 105 stores information processed by systems-biology platform 104. Data storage 105 may be located internally or externally relative to the organism, which can be accessed through wireless communication unit 106.

Regulation software or overlay 320 couples to data storage 105. When systems-biology platform 104 communicates with data storage 105, regulation overlay 320 assures that therapies, instructions, or other communications complies with Food and Drug Administration (FDA), Patent and Trademark Office (PTO), or other government regulatory bodies.

Regulation overlay 320 can store information or instructions for private agreements or regulations, such as

contract or licensing agreement between biosensor 100 and pharmaceutical company. Depending on the severity of the organism's condition or systems-biology platform 104 suggested therapy, communication directly or indirectly with FDA may be possible in instances where "expanded access," "compassionate use," "well characterized biological products," and other FDA exceptions apply. FDA may respond favourably and allow use of unapproved therapy (suggested by systems-biology platform 104) if exceptions apply.

Systems-biology platform 104 may implement a neural network to model a biological system or serve as a decision aid for medical applications, problems or diagnosis. For example platform 104 may employ methods such as pattern recognition, feature extraction, supervised learning, unsupervised learning, or learning algorithms. Supervised learning methods may include Fisher's Linear Discriminant, Gradient Descent Procedures, the Perceptron Algorithm, Relaxation Procedures, or Potential Functions for linearly separable sets, or Nonlinear Discriminant Functions, Hypernet, Minimum Squared Error Procedures (MSE), or the Ho-Kashyap Procedure for nonlinearly separable sets.

For multiple category classification problems, supervised learning methods may include the Fisher Linear Discriminant, Kesler Construction, or Backpropagation. Unsupervised learning methods may include clustering, Kohonen networks, Kohonen Competitive Leearning, Hebbian learning, Adaptive Resonance Theory (ART) or prototype distribution map (PDM). Clustering approaches may include the Basic Isodata Procedure, a similarity measure approach, or criterion functions.

Criterion functions approaches may further include sum of squared error criteria, minimum error criteria, or scattering criteria, and such criteria may be used in an iterative optimization procedure. Platform 104 may also employ clustering approaches such as hierarchical clustering or metrics.

To assist in medical decision-making, systems-biology platform 104 may implement artificial intelligence or decision techniques, particularly data-based techniques or knowledge-based techniques. Data-base techniques may include approaches such as database decision theory, pattern recognition, or Bayesian analysis, while knowledge-based techniques may include mathematical modeling and simulation, symbolic reasoning, as well as databases.

Systems-biology platform 104 may employ databases such as patient record structures (e.g., hierarchical databases, National Library of Medicine, MUMPS (Massachusetts General Hospital Utility Multi-Programming System), the ARAMIS system, PROMIS (problem-oriented medical information system), or a medical database management system (e.g. MEDUS/A)). Systems platform 104 may employ a disease database (e.g. oncology, rheumatology), or decision-support system (e.g. the HELP program).

Platform 104 may employ a differential diagnosis database (e.g. RECONSIDER or DXplain), an online database, a radiological database (e.g. CHORUS (collaborative Hypertext of Radiology)), or the Human Genome Project. Mathematical modeling and simulation may apply to modeling of the organism

or a biological process. The biological process may be represented by mathematical equations and evaluated.

Simulation involves representation of the organism or biological process on a computer. Mathematical formulation may apply to administration of drugs or analysis of drug toxicity or drug level in a biological system. Pattern-recognition techniques may include discriminant analysis, methods of classification using Bayes' Rule, parameter estimation, supervised learning or unsupervised learning.

Unsupervised techniques may include Parzen windworks, k-nearest neighbour estimation or other learning clustering techniques. Decision theory techniques may employ Bayesian analysis or Markovian analysis. Symbolic reasoning techniques may employ knowledge-based expert systems including early expert systems, and second-generation expert systems. Techniques of expert systems may include knowledge representation, heuristic search, natural language understanding, and exact reasoning. Second-generation expert systems may employ casual models, reasoning with uncertainty, or hybrid systems.

Systems-biology platform 104 may implement fuzzy techniques, (e.g. fuzzy set theory, fuzzy logic, fuzzy variables, or membership functions) for use in neural networks and expert systems. In dealing with uncertainty in supervised learning networks, neural networks may further employ pre-processing of fuzzy input, propagation of results through the network, or interpretation of final results.

Propagation of results may employ max-min networks, learning algorithms for interval data, or analogue models. Unsupervised learning methods may employ fuzzy associative memories or fuzzy clustering. Fuzzy methods for use in clustering include relation criterion functions, object criterion functions, fuzzy isodata, convex decomposition, numerical transitive, generalized nearest neighbour rules, or the HCM/FCM clustering algorithm.

Uncertain information in a knowledge-based system may employ fuzzy techniques when dealing with uncertainty in relation to input data, knowledge base, inference engine (e.g., binary logic engines or fuzzy logic engines), evidential reasoning (e.g., possibility theory, probabilistic approaches, or Dempster-Shafer Belief Theory), compatibility indices, or approximate reasoning.

Alternatively systems-biology platform 104 may employ probabilistic systems or statistical analysis for analysis of medical data. Probabilistic systems may include Bayesian approaches, parameter estimation, discriminant analysis, statistical pattern classification, unsupervised learning, or regression analysis.

Bayesian approaches may include Bayes' Rule, Bayes' Decision Theory, risk analysis, supervised Bayesian learning, or decision trees. Parameter estimation may include maximum likelihood estimation or Bayesian estimation. Unsupervised learning may include Parzen window approach, nearest-neighbor algorithm, mixture densities and maximum likelihood estimates, unsupervised or Bayesian learning.

For example systems-biology platform 104 receives raw data from sensor unit 111 and employs neural networks, artificial intelligence, fuzzy systems, or probabilistic systems to aid in medical decision making for therapy recommendations or diagnosis.

Optionally additional information or test data helpful for diagnosis or treatment may be gathered from electronic files or user input from an outside source via and stored in data storage 105. Additional information or test data may include: patient age, height, weight, symptoms, allergies, diet, previous or present medications, medical or family history of disease, sickness or infection, results of previous blood, urine or other bodily fluid analysis, or other nongenetic (e.g., environmental) or immunological factors relating to the patient.

Optionally systems-biology platform 104 sends therapy recommendations or diagnosis report to an outside source via wireless communication 106 and stores recommendations or a report in data storage 105.

In clinical, managed-care, hospital, diagnostic, therapeutic, or biomedical applications or embodiments, systems-biology platform 104, using one or more of firmware, source or object code software, a configurable logic chip or device, a digital signal processor, a systolic processing array, or other finite state machine, actually or effectively may compare a set of bioinformatic values associated with a sensor signal or simulation data, preferably associated with the same or different temporal states, to determine or otherwise recognize one or more genomic mutations associated

with or corresponding to a target patient, animal, plant, or other biological host.

Furthermore systems-biology platform 104 may operate autonomously, in cooperation with other computer system nodes, clients, or processing elements, to collect, process and display various host or patient sensor or simulation data, preferably in combination.

For example patient information and other personal or medical record data such as host identification, drug treatment, prescription, and dosage, single or multiple concomitant food or drug allergy, interaction or side effect, pregnancy, lactation, as well as bioinformatic, genetic, proteomic, metabolomic, and other monitored, simulated or sensed mutation-related data as described herein may be received via questionnaire or otherwise retrieved.

Systems-biology platform 104 may be used in a time-critical emergency, urgent, or trauma situation to improve patient health-care diagnosis and treatment, for example, by early-detection, expediting and assisting the physician, or paramedical or nursing staff or by expediting and assisting other professional analysis and treatment.

A sensed signal or simulated data may be electronically labeled for indicating genomic mutation, and significantly improves the quality and accuracy of medication delivery and administration to identified subgroups of patients having certain adverse responses to medication, food, or other treatment.

Additionally such data or signal may include pharmaco-genomic or pharmaco-kinetic clinical or indications based on genetic, proteomic, metabolomic (i.e., analysis of small organic cell molecules and metabolic response thereof), or other bioinformatic variants or mutations, or other genetic-based conditions or profiles (e.g., sex, race/ethnicity, etc.) such as drugs to be avoided, or considered as an alternative. Thus, optimally, the host's susceptibility or predisposition to toxicity or other adverse reaction to or side effects arising from certain identified food, drugs, or other medical treatment may be minimized, mitigated, or eliminated using automated rule-based advice or an expert system.

For example, systems-biology platform 104 may alert medical professionals when it is determined via a sense or simulation approach to detecting genomic mutation that the patent's ability to produce thiopurine S-methyltransferase (TPMT) enzyme activity is compromised. The TPMT genetic test (commercially available from DNA Sciences (Raleigh, NC)) enables identification of patients at risk for 6-MP/azathioprine/thioguanine toxicity, and improves confidence through tailored dosing regimens, while minimizing concern over drug-induced complications.

Alternatively, genomic mutation to G protein-coupled receptors (GPCR), molecular targets and variant alleles may be detected to electronically label and thereby effectively modify the host drug therapy. Another genomic mutation that may be detected and labeled is enzyme debrisoquine hydroxylase (CYP2D6), an isozyme of the microsomal cytochrome P450 monooxygenase system; the encoding gene is located in

the CYP2D gene cluster in a contiguous 45-kb region of chromosome 22. Here, at least nine polymorphisms of CYP2D6 affect the metabolism of more than 30 different pharmaceuticals, including β-adrenergic receptor antagonists, neuroleptics, and tricyclic antidepressants.

Systems-biology platform 104 may couple electronically or digitally to a hospital, physician, nursing, or other medical staff communication system to enable network-accessible prescription renewal, appointment scheduling, lab-result entry or retrieval, referrals to specialists and disease management, as well as generally computerized physician or pharmacy-ordering schemes, patient communications, access to medical simulation, test or sensor results, insurance claim status, and bar-coding of pharmaceuticals, and automated medication checks for possible errors.

System-biology platform 104 may employ simple identical or substantial equivalent value checks between recently-measured values and previously-stored values for the same host, for example, after host exposure to radiation or other carcinogenic sources.

Such an algorithm may be executed to adapt iteratively or dynamically in real-time or in multiple or parallel processors based on currently or recently-measured, monitored, or sensed host bioinformatic values, for example using a fuzzy system, Bayesian or neural network, to improve computing or processing performance by comparing initially values that previously are known or recorded to be related or

likely to be related or otherwise weighted to sensor signal or simulation data.

Additionally electronic access to sensor signal or simulation data may be restricted, secured, encrypted, or excluded unless the host thereof explicitly or voluntarily provides prior informed consent to access such information.

Hence, the comparison serves to detect the presence or absence of a target sensor signal, simulation data or other genomic or bioinformatic values (e.g., oncogene, tumor suppressor gene, allele, enzyme, repeat sequence, micro-deletion, or other mutant gene product, protein, or metabolome) that cause or increase or decrease the risk of one or more host diseases, disorders, syndromes, allergies, or other biological conditions.

Such simulation data or sensor information may be stored in data storage 105 or in other digital storage accessible or otherwise retrievable through network 103. Such stored information may be formatted according to one or more conventional, industry-standard, or otherwise publicly or commercially-available software, processing, storage, and communications protocols, as well as databases for metabolic, signaling, regulatory and pathway data.

Additionally other genomic relational or object-oriented knowledge bases or data sources may be network-accessed, such as GenBank, Unigene, LocusLink, Homologene, Ensemble, GoldenPath, or NCICB Cancer Genome Anatomy Project (CGAP). Such information may be accessed using ontology-based interfaces that are defined to be logically related, for

example, using an annotation format such as the Distributed Annotation System (DAS).

Optionally systems-biology platform 104 data or instructions may be specified and otherwise annotated, such as with a hypothesis definition, experiment design, sample preparation and distribution, experiment run, data acquisition, result analysis, data mining, design refinement, modeling, knowledge discovery, or project report. Additionally such functions may be applied to simulation data or sensor signals processed by software or hardware analysis tools, e.g., for pharmacogenomics, gene expression, high-throughput sequencing, or proteomics (functional or structural) use-case domains.

Preferably such stored information complies, at least in part, with data exchange and management framework and specifications provided by the Interoperable Informatics Infrastructure Consortium (I3C), which technical and use-case model documents, and recommended implementations, are described on-line at http://www.i3c.org/ and hereby incorporated by reference as appropriate herein.

For example, one or more I3C-compliant or recommended data formats may be employed during operation of an electronic label processor, as described herein. Accordingly simulation data or sensor signals may be accessed, and displayed or otherwise imaged using electronic display I/O hardware or software, for gel chromatography images, original data from biological arrays, arrays of time-series data from mass spectrometry, illustrative functional depiction of proteins, simple microscope images, patient records with

medical images, derived data from multiple or time-series images, electrocardiograms, or original drawings and annotations to medical images made by examining professionals. On-screen search capability enables a medical professional quickly to locate and interpret particular host simulation data or a sensor signal, such as a gene sequence, protein, enzyme, allele, or other related detail.

Network 103 access to various databases or other digital repository may couple in n-tiered architecture multiple client interfaces, serve components, back-end objects and data sources. For example, Linux-based, Netscape, or Microsoft Internet Explorer browsers or applications, e.g., based on Java, non-Java, Perl, C, C++, or other programming or development software, run on client nodes 60 may receive information, in e.g. various mark up languages e.g., HTML, XML, etc., from back-end objects over conventional network messaging or transport protocols, e.g., hyper text transfer protocol (HTTP), TCP Internet Protocol, simple object access protocol (SOAP), file transfer protocol (FTP), IIOP, etc. additionally Universal Description Discovery Integration (UDDI) registry and Resource Description Framework (RDF) agent advertising formats may be used.

Further a genomic, proteomic, or metabolomic sequence analysis software tool, for example, (e.g., BLAST, TimeLogic) may be used by controller 112 to discover or characterize a host is genomic, proteomic, or metabolomic sequence, acquired and qualified from one or more sources, such as sensor unit 111 or data storage 105. Thus, internal and external sequence and protein libraries may be updated and maintained, certain redundant, unqualified or external data being filtered for

internal sequence processing. One or more target, putative or otherwise mutant gene or bioinformatic value is then determined and catalogued effectively by systems-biology platform 104.

Hypothetical function of such determined genes or values may be generated manually, automatically, or homologously by finding similarity to known or other prior values. Genetic, proteomic, or metabolomic analysis protocols and similarity analysis may bc defined and selected, thereby enabling or constructing functional hypotheses to be generated, prioritized, or reviewed using sensor measurements or other host evidence.

Proteolysis sample preparation may be performed (e.g., HPLC, gel electrophoresis), then mass spectroscopy or tandem MS analysis and compression, quantitization, and fragment size genome analysis for candidate prediction, proteome or metabolome comparison, and other quantitative analysis using modeling tools and databases.

Systems-biology platform 104 may receive data from sensor unit 111, and neural networks, artificial intelligence, fuzzy systems, or probabilistic systems which consider presence of conditions in diagnosis of genetic disorders: point mutations, mutations within non-coding sequences, deletions and insertions, trinucleotide repeat mutations, autosomal mutations, gain of function mutations, loss of function mutations, mutations in mitochondrial genes, enzyme defects, defects in receptors and transport systems, defects in receptors and transport systems, alterations in structure, function or quantity of non-enzyme proteins,

defects in receptor proteins, defects in protooncogenes or tumor-suppressor genes, aneuploidy, unbalanced autosome, sex chromosome abnormality, fragile X syndrome, ring chromosome, chromosome inversion, isochromosome formation, translocation, or abnormal gene products.

Optionally allele-specific oligonucleotide hybridization may be employed in multifunctional array 200 in biosensor platform 102 to assist in direct gene diagnosis of mutations. Systems-biology platform 104 may diagnose genetic diseases or mutations, such as Mendelian disorders, autosomal dominant disorders, autosomal recessive disorders, X-linked disorders, Marfan syndrome, Ehlers-Danlos syndrome, familial hypercholesterolemia, lysosomal storage diseases, Tay-Sachs Disease, Gangliosidosis, Niemann-Pick disease, Gaucher Disease, glycogen storage diseases, Mucopolysaccharidoses, Alkaptonuria, Neurofibromatosis, trisomy 21, chromosome 22q11 deletion syndrome, Klinefelter syndrome, XYY syndrome, Turner Syndrome, Multi-X females, hermaphroditism, pseudohermaphroditism, triplet repeat mutations, chromosome-breakage syndrome, Prader-Willi syndrome, Angelman syndrome, or gonadal mosaicism.

Alternatively, systems-biology platform 104 may diagnose infections diseases or infections such as Haemophilus influenza infection, tuberculosis, histoplasmosis, coccidiodomycyosis, shigella bacillary dysentery, Campylobacter enteritis, Yersinia enteritis, Salmonellosis, typhoid fever, cholera, amebiasis, giardiasis, herpes, Chlamydia, gonorrhea, syphilis, trichomoniasis, staphylococcal infection, streptococcal infection, clostridial infection, measles, mumps, mononucleosis, polio,

chickenpox, shingles, whooping cough, diphtheria, infections associated with Neutropenia and Helper-T cell depletion, cytomegalic inclusion disease, pseudomonas infection, legionnaires disease, listeriosis, candidiasis, cryptococcosis, aspergillosis, mucormycosis, pneumocystis, pneumonia, cryptosporidium and cyclospora infection, toxoplasmosis, dengue fever, Rickettsial Infection, trachoma, leprosy, plague, relapsing fever, lyme disease, malaria, babesiosis, leishmaniasis, African Trypanosomiasis, Chagas disease, Trichinellosis, hookworm, cysticercosis, Hydatid disease, chistosomiasis, lymphatic filariasis, or onchocerciasis.

In diagnosing infectious disease or infection, systems-biology platform 104 receives data from sensor unit 111 or neural networks, artificial intelligence, fuzzy systems, or probabilitic systems that consider the presence of an infectious agent, such as a prion, virus, bacteriophage, plasmid, transposon, chlamydiae, rickettsiae, mycoplasma, fungi, protozoa, helminths, or ectoparasite. In the host system, systems-biology platform 104 may also consider the presence of bacterial endotoxin, bacterial exotoxins, proliferation andmorphologic lesions of epithelial cells, tissue necrosis, granulomas, cysts, increased levels of leukocytes, mononuclear cells or neutrophils, mononuclear interstitial infiltrates, reduced levels of immune cells (e.g. cytokines, lymphocytes, macrophages, dendritic cells or natural killer cells), bacterial leukotoxins, hemagglutinin, spores, or other antigens or proteins from bacteria, virus, fungi, protozoa, or parasite.

Alternatively systems-biology platform 104 may diagnose diseases of immunity, such as hypersensitivity disorders (immune complex mediated, complement-dependent reactions, cell mediated, or anaphylactic type, transplant rejection) autoimmune disease, systemic sclerosis, inflammatory myopathies, mixed connective tissue disease, polyarteritis nodosa or other vasculitides, X-linked agammaglobulinemia of Bruton, common variable immunodeficiency, isolaged IgA deficiency, Hyper IgM syndrome, DiGeorge syndrome, severe combined immunodeficiency disease, immunodeficiency with thrombocytopenia and eczema, acquired immunodeficiency syndrome (AIDS), or amyloidosis.

In diagnosing immunity diseases, systems-biology platform 104 considers the following sensed, detected, or measured conditions from sensor unit 111: levels of immune cells (e.g., mast cells, cytokines, lymphocytes, macrophages, dendritic cells or natural killer cells), MHC (major histocompatibility complex) molecules or antigens, HLA (human leukocyte antigen) complex, antigens, or types, or levels of primary mediators(e.g., biogenic amines, chemotatic mediators, enzymes, or proteoglycans), secondary mediators (e.g., leukotrienes, prostaglandins, platelet-activating factors, or cytokines), histamines, platelet-activating factor (PAF), neutral proteases, chemotactic factors, or antigen-presenting cells (APC).

In diagnosing autoimmunity diseases, systems-biology platform 104 receives data from sensor unit 111 or neural networks, artificial intelligence, fuzzy systems, or probabilistic systems and considers the presence of auto-antibodies disease and considers whether auto-antibodies are

directed against a single organ or cell type or whether the disease is systemic. Autoimmune diseases include single organ or cell type related diseases (e.g., hashimoto thryoiditis, autoimmune hemolytic anaemia, autoimmune atrophic gastritis of pernicious anaemia, autoimmune encephalomyelitis, autoimmune orchitis, goodpasture syndrome, autoimmune thromcytopenia, insulin-dependent diabetes mellitus, myasthenia gravis, Graves disease), or systemic autoimmune diseases (e.g., systemic lupus erythmatosus, rheumatoid arthritis, Sjögren syndrome, or Reiter syndrome).

Systems-biology platform 104 may identify whether the disease condition is a single organ or cell type autoimmune disease or primary biliary cirrhosis, chronic active hepatitis, ulcerative colitis, or membranous glomerulonephritis. The platform is also identifies whether the disease condition may be a systemic autoimmune disease or involve inflammatory myopathies, systemic sclerosis (scleroderma) or polyarteritis nodosa.

Furthermore systems-biology platform 104 may determine the presence of pathologic autoimmunity by considering at least three requirements, such as the presence of an autoimmune reaction, clinical or experimental evidence that such reaction is not secondary to tissue damage but of primary pathogenetic significance, or absence of another well-defined cause of disease.

Alternatively systems-biology platform may be used in diagnosis of neoplasia. In diagnosing neoplasia, systems-biology platform 104 receives sensed, detected, or measured data from sensor unit 111 and neural networks, artificial

intelligence, fuzzy systems, or probabilistic systems and considers the following factors: DNA damage, failure of DNA repair, mutations in the genome of somatic cells, activation of growth-promoting oncogenes, alterations in the genes that regulate apoptosis, inactivation of cancer suppressor genes, expression of altered gene products and loss of regulatory gene products, oncoproteins, growth factors, growth factor receptors, proteins involved in signal transduction, nuclear regulatory proteins, cell cycle regulators, tumor antigens, or the levels of immune cells (e.g., mast cells, cytokines, lymphocytes, macrophages, dendritic cells or natural killer cells).

Systems-biology platform 104 may consider epidemiological factors in determining diagnosis for neoplasia. Epidemiological factors may include cancer incidence, geographic or environmental factors (DNA damaging agents - e.g. chemicals, radiation or viruses), or heredity (e.g., inherited cancer syndromes, familial cancers, autosomal recessive syndromes of defective DNA repair). Systems-biology platform 104 may consider tumor markers such as hormones (e.g. human chorionic gonadotropin, calcitonin, catecholamine and metabolites, or ectopic hormones), oncofetal antigens (α-fetoprotein or carcinoembryonic antigen), isoenzymes (e.g., prostatic acid phosphatase, or neuron-specific enolase), immunoglobulins, prostate-specific antigens or mucins or other glycoproteins (e.g. CA-125, CA-19-9, or CA-15-3).

After systems-biology platform 104 makes a diagnosis, the platform may recommend treatments in combination or individually. Such recommendation may include diet changes,

surgery, radiation therapy, chemotherapy, medications, antiangiogenesis therapy, or other cancer treatment. Systems-biology platform 104 may instruct therapeutic unit 113 to manufacture or dispense pharmaceuticals, biopharmaceuticals, or other therapeutic tools for the treatment of neoplasia.

Systems-biology platform 104 may employ sensor device and simulation methods for analyzing dynamic hormone-secretion phenomena in dynamic biological systems, for example using a sensor, artificial neural network, and dosing device; e.g., the Sicel Technologies wireless or telemetric sensor platform for measuring parameters of relevance in vivo, such as radiation dose, tissue microenvironment or gene expression to increase treatment success. Implantable sensors 2mm in diameter, 15mm in length, may be provided for injection at the margin of tumors using a minimally invasive procedure.

Biosensor 100 may be applied to food technology, e.g., pasteurization or development or production of foods. DNA sensor 201 may monitor, detect, or measure the amount of bacteria or microflora used to ripen and develop flavours in foods, such as cheese. Similarly peptide or protein sensor 203, lipid or fatty acid sensor 208, or small molecule sensor 217 may monitor bacterial or microflora production of fats, proteins, esters, or other biologically-active molecules.

Biosensor 100 may be applied to the food manufacturing industry, e.g., quality control, food safety, or countering food borne illness caused by bioterrorism. Biosensor 100 may detect types of food contaminants, including bacteria or

chemicals that cause human sickness, or counter bioterrorism acts threatening consumer food supply.

Biosensor 100 may be used by a food manufacturer, crop cultivator, lab researcher, consumer, packer, distributor, receiver, food vendor, or food inspector to ensure quality control and food safety. Biosensor platform 102 may detect, measure, or determine presence or absence of parasitic organism, virus, bacteria, fungi, protozoa, or unicellular or multi-cellular organism present during food manufacturing process or growth of food crops, or prior to consumption.

Chemical sensor 216 may be used to sense, detect, or measure foreign chemicals, such as toxins, vitamins, minerals or other organic and inorganic chemicals. Systems-biology platform 104 may analyze raw data from biosensor platform 102 to identify a potentially-hazardous organism or chemical or flag unknown organism or chemical.

When systems-biology platform 104 identifies or quantifies a potentially hazardous organism or chemical or unknown organism or chemical, data is stored in storage 105. Systems-biology platform 104 may generate a report document or electronic multi-media warning or signal, which discloses the detected organism or chemical and determines whether it is safe to continue manufacturing, crop growth, or consumption.

Systems-biology platform 104 may send an automated warning or signal, sent via wireless communication 106, to an information recipient interested in data gathered by the platform, such as a remote database, researcher, lab,

government agency, or health or safety maintenance organization.

Chemical sensor 216 may determine the purity or verify the amount of vitamin, mineral, herb, or botanical claimed by a food product, meal supplement, vitamin supplement, or other nutritional substance. Systems-biology platform 104 may compare the amount of vitamin, mineral, herb or botanical determined by chemical sensor 216 with a pre-set amount or range stored in storage 105, e.g. an amount or range determined by a government agency or health or safety maintenance organization.

Systems-biology platform 104 generates a report on whether the detected amount or range complies with a pre-set amount or range, and determines whether it is safe to continue manufacturing or consumption. The detected amount can be reported and sent via wireless communication 106 to an outside source or information recipient interested in data gathered by chemical sensor 216, such as a packer, distributor, receiver, remote database, researcher, lab, government agency, or health or safety maintenance organization. During manufacturing, a determined amount of a vitamin, mineral, herb, or botanical present in each lot or batch of produced product is recorded or accessible through network 103 for analysis.

Optionally if the amount of vitamin, mineral, herb, or botanical falls outside the pre-set amount or range, systems-biology platform 104 generates an automated warning to the outside source or information recipient. Biosensor 100 monitors the manufacturing of the food product, meal

supplement, vitamin supplement, or other nutritional substance by ensuring that the manufactured substance complies with the required amount or range of nutritional substance. Chemical sensor 216 may be used to demonstrate whether a particular vitamin, mineral, herb, botanic, or other natural or organic food has been properly absorbed in the biological system of an organism.

Biosensor 100 may synchronize different input stimuli, particularly with the integrated purpose of evaluating food and drug interactions positively or negatively within a host. Systems-biology platform 104 can analyze the genetic composition of the host, determined through DNA sensor 201, to assist in predicting particular drug-food interactions. To assist in predicting drug and food interactions, the host genetic composition may be supplemented with additional information or test data including nongenetic (e.g. environmental, epidemiological) or immunological factors relating to the host.

Biosensor 100 may be implanted within a host and pharmacogenetics 304 or pharmacokinetics 308 in systems-biology platform 104 may be employed to monitor or determine the activity or effectiveness of medication used individually or in combination. Meanwhile, biosensor 100 placed remotely or separately from an implanted biosensor is used to analyze a nutritional substance (e.g., a food product, meal supplement, vitamin, or mineral) that may be consumed by same host.

Data from remote biosensor 100 is coupled to, received from, or combined with data from the implanted biosensor or

analyzed collectively by systems-biology platform 104 to predict or model combined allergic reactions, side effects, or adverse reactions that result from consumption of the nutritional substance at the same time as related medication.

Systems-biology platform 104 may generate an automated recommendation or report diagnostically or therapeutically about the optimum level of nutritional substance or identify an alternative substance for consumption. Data from a remote location, and implantable biosensor data, and a recommendation or determination processed by systems-biology platform 104 may be stored in data storage 105. An outside source or information recipient may access data and results in data storage 105 through wireless communication 106 for analysis via network 103.

When systems-biology 104 identifies a nutritional substance that may cause an adverse or positive reaction, an automated warning or message may be transmitted wirelessly to an information receipt interested in the gathered data. The ability of the systems-biology platform to analyze or model the nutritional substance and host condition in combination using host sensor data and consumable sensor data optimizes treatment of a real-time physiological condition.

Biosensor 100 may be applied to biopharming purposes, e.g., field tests or inspections of genetically engineered plants, and use of genetically engineered plants or transgenic crops to produce therapeutic proteins and industrial enzymes with safeguards for ensuring that food crops are not co-mingled with food crops intended for pharmaceutical or industrial use.

To prevent out-crossing or commingling of genetic material, DNA sensor 201, RNA sensor 202, or peptide and proteins sensor 203 in biosensor platform 102 may detect, sense or measure presence or absence of foreign genetic material or protein in a food crop not intended for pharmaceutical or industrial use. Systems-biology platform 104 may analyze raw data from biosensor platform 102 to identify out-crossing or commingling of genetic material.

When systems-biology platform 104 identifies foreign genetic material, data is stored in storage 105. Systems-biology platform 104 may generate a report about detected foreign genetic material or determine whether crop growth is safe to continue. Systems-biology platform 104 may send an automated warning or signal, via wireless communication 106, to an information recipient interested in data gathered by the platform, such as a remote database, researcher, lab, government agency, or health or safety maintenance organization.

Biosensor 100 may monitor growth of food crops. For example, sensors (e.g. peptide or protein sensor 203, vector or virus vector sensor 207, pH sensor 212, metabolites sensor 219, etc.) in biosensor platform sensor 201 may sense, detect or measure abnormalities in crop growth or reproduction. Biosensor 100 may monitor, detect or measure the effect on growth or reproduction of pesticides, insecticides or foreign chemicals.

Biosensor 100 may be applied to bio-manufacturing industry, e.g., drug-producing plants and transgenic animals,

such as cows genetically transformed to excrete different kinds of therapeutic proteins in breast milk. Peptide or protein sensor 203 in biosensor platform 102 or antibody sensor 204 may detect or measure the presence or absence of a genetically engineered therapeutic protein or antibody in breast milk or other biological fluid.

Biosensor 100 may be applied in xenotransplantation, for example by screening animal organs for transplantation into humans. Sensor unit 111 senses, measures, or processes biological molecules, such as cell, tissue, or intracellular or extracellular material from an animal cell, tissue or organ, or raw data is analyzed by system biology platform 104. System biology platform 104 analyzes or determines whether the animal cell, tissue, or organ is compatible for use with humans for transplantation or other therapeutic process.

Biosensor 100 may be applied to avian transgenics, particularly to proteins produced through poultry-based production systems. For example, biosensor platform 10 may detect whether successful transformation is occurring via avian embryonic germ cells, retroviral-mediated transformation, sperm-mediated transgenesis, avian embryonic stem cells, direct egg transfection, or other transformation processes.

Biosensor 100 may be applied to drug-producing plants, e.g. tobacco, corn, or other non-food plants, for biomanufacturing. Peptide or protein sensor 203 may detect, sense or measure the presence, absence, manufacture or biological activity of recombinant proteins manufactured in

plants. DNA sensor 201, RNA sensor 202, vector or virus vector sensor 207, chromosome sensor 221, or cell sensor 222 may monitor or detect whether genetic material, or a vector, chromosome, or cell successfully integrates or genetically transforms a plant or animal.

Figure 3c shows systems-biology platform 104, therapeutic unit 113, and sensor unit 111. Systems-biology platform 104 provides verification of data 321, to assure that the data is proper or feasible from biosensor platform 102 within sensor unit 111. Verification of data 321 identifies a sequence or structures of a target system. Data may be analyzed statistically by systems-biology platform 104, using statistical computation, e.g., scatter plot matrices, Venn diagrams, comparative histograms, volcano plots, or gene ontology charts. Computed statistics are interpreted biologically, filtering or reducing the dataset to a manageable size by eliminating results that show insignificant or uninteresting biological data.

Verification of data 321 includes checking regulatory relationship of genes or interaction of proteins that provide signal transduction or metabolism pathways, as well as the physical structure of organisms, organelles, chromatins, cell-cell interactions, or other components.

To integrate sensor data, software and management systems are used. Systems-biology platform 104 may utilize management software, e.g., Analysis Information Management System (AIMS), using tools to analyze or manage range of complexity of data obtained from microarrays or assays, tracking computational processes. Data-mining tools, e.g.,

high-dimensional data analysis tools, may process the data where the data has multiple dimensions.

Data may be formatted using standardization programs, e.g., Gene Expression Markup Language (GEML), Mircroarray Markup Language (MAML), Microarray and Gene Expression Data (MAGE), MircoArray and Gene Expression Markup Language (MAGE-ML), solutions by Microarray Gene Expression Database group (MGED) or Minimum Information About a Microarray Experiment (MAIME), or other programs.

After the data is verified, modeling/simulation 322 uses combined simulation data or sensor signals to model biological structures or mutual interactions. Modeling or simulation 322 simulates biological interactions to identify the behaviour of a system, for example, sensitivity of behaviours against external perturbations and how quickly the system returns to a normal state after stimuli.

Another example includes simulating how an individual malfunctioning mis-folded protein interacts with other proteins or cellular components, with simulations on how the protein responds to particular therapies; yet another example is modeling phospho-proteomics and a system's biological role for oncology target discovery or validation.

Modeling or simulation 322 predicts methods of controlling the state of a biological system, e.g., pharmaceutical or gene therapy transformation of malfunctioning cells into healthy cells. For example through structural analysis, regulation of c-Abl and STI-571 specificity may be achieved.

Modeling or simulation 322 prediction is translated into instructions for therapeutic unit 113 to implement appropriate therapy to fix a biological system. These instructions are conveyed to therapeutic unit 113, where instructed therapy may be performed.

Sensing unit 111 monitors the progress, efficiency, or ancillary effects of the induced therapy on the biological system. Data from sensing unit 111 may be verified by verification of data 321, which provides a cyclical self-regulating process.

Figure 4a shows the flow of instructions from systems-biology platform 104 to network 103 to components comprising therapeutic unit 113. Components of therapeutic unit 113 include therapeutic manufacture 108, therapeutic reservoirs 109, and a reconfigurable sensor manufacturer 110. These components may be reconfigurable or software-programmable according to systems-biology platform 104, or from a external source through wireless communication unit 106.

Figure 4b shows therapeutic manufacture 108 of: pharmaceuticals 401, biopharmaceuticals 402, tissue, reconfigurable biocatalytic chips 403, tissue scaffolds 404, M/N machines 405, or other therapeutic material or tools. These components may be reconfigurable and software-programmable according to systems-biology platform 104, or from an external source through wireless communication unit 106.

Pharmaceuticals 401 may be known and matched with an organism, or computationally derived or optimized from systems-biology platform 104. Pharmaceuticals 401 is defined herein as including a chemical substance that provides benefit to a system.

Biopharmaceuticals can be naturally-occurring biological molecules or structural derivatives of biological molecules. For example, biopharmaceuticals can be isolated DNA molecules, recombinant DNA molecules, DNA fragments, oligonucleotides, antisense oligonucleotides, RNA molecules or constructs, self-modifying RNA molecules, catalytic RNAs, ribozymes, modified ribozymes, synthetic peptides, peptide linkers, proteins, fusion proteins, antibodies, modified antibodies, antigens, cell surface receptors, monoclonal antibodies specific for epitopes, polyclonal antibodies, tissue factors, modified tissue factors, mutant tissue factors, ligands, vectors, virus strains for gene transfer, recombinant plant viral nucleic acids, bacterial strains, oil-body proteins as carries of high-value peptide in plants, host cells, transformed cells, or microorganisms newly isolated in pure form from a natural source.

Therapeutic unit 108 may prepare biopharmaceutical product such as 2 νg of sub50-nm tenascin nanocapsules containing antisense of protein kinase CK2 α subunit or similarly GFP and RFP-labeled bacteria which produce toxins or other therapeutic proteins to be used to target tumors. Further therapeutic unit 108 can perform functions such as the so-called Intelligent Pill (e.g., University of Calgary) in which information is relayed to a chip that controls micropumps that squeeze-out therapeutic material.

Therapeutic manufacture unit 108 may prepare therapy comprising a pharmaceutical 401 or biopharmaceutical aspect 402. For example antiangiogenesis thereapy using yttrium-90 nanoparticles with conjugated anti-Flk-1 monoclonal antibody administered by i.v. injection can be used for treatment of solid tumors. Therapeutic manufacture unit 108 may produce small interfering RNA (siRNA) used to inhibit P-gp encoded by *MDR1* gene; production enhances the accumulation of sensitivity of multidrug-resistant cancer cells to drugs transported by P-glycoprotein.

Reconfigurable biocatalytic chips 403 are software programmable from instructions by systems-biology platform 104, or from an external source through wireless communication unit 106. Depending on the instructions, reconfigurable biocatalytic chips 403 can be activated, deactivated, manufactured, or disassembled. Reconfigurable biocatalytic chips 403 carry out molecular bioprocessing, fabricating or manipulate single and multienzyme systems on biochip to induce artificially biocatalysis in a system.

Tissue scaffolds 404 may be reconfigurable, and controlled by instructions from systems-biology platform 104 (or from an external source through wireless communication unit 106). Scaffold 404 may be a substrate to grow cells or tissues, which may be activated or deactivated according to signalled instructions. Permanent or biodegradable tissue scaffolds can be used. Further scaffold 404 may be personalized by systems-biology platform, e.g., the John Hopkins University stem cell-based polymer scaffolds for tissue engineering using composite hydrogel. After modeling

tissue development on biomaterial scaffolds based on an individualized systems-biology profile, reconfigurable scaffold 404 can be programmed with biological signals based on individual need.

M/N tools 405 may perform therapeutic treatments, e.g., obtainable from Johnson & Johnson Cordis Corporation, that make drug coated stents that keep arteries from clogging by releasing medication. Examples of M/N tools may be self-assembling, e.g., Angstrom Medica altered calcium and phosphate molecules that self-assemble to create nanostructured synthetic bone.

Another tool example is the S. Stupp project at Northwestern University, which provides long complex molecules with hydrophobic tails and hydrophilic heads; these molecules self-assemble to form cylindrical structures that can be applied to making artificial bone. Another example of M/N tools 405 is the Son Binh Nguyen use of nanoparticles for small molecule chemotherapy, in which engineered hydrophobic cyclic peptides attaches to targeted molecules and subsequently chemically react with the molecule, breaking it into pieces.

Figure 4c shows components of therapeutic reservoirs 109. Release of therapies is dictated or controlled by instructions from systems-biology platform 104 or from an external source through wireless communication unit 106; timing mechanisms or rate of release may be reconfigured by software, e.g., MicroCHIPS implantable bioMEMS for drug delivery, in which silicon reservoirs hold medications in solid, liquid, or gel form, or iMEDD "NanoPORE Membranes,"

silicon wafers that have channels or pores with dimensions on the nanometer scale for drug release.

Pre-filled reservoirs 410 are contained in medication filled-in biosensor 100 before implantation in living system. The contents of pre-filled reservoirs 410 may be pharmaceuticals or biopharmaceuticals in active form for release directly to a living system. Pre-filled reservoirs 410 may hold probes, amino acids, nucleotides, or building blocks for sensor manufacture 110 for making additional biosensors.

Precursors 411 may be biological and chemical precursors to therapeutic pharmaceuticals and biopharmaceuticals. Depending on the instructions from systems-biology platform 104, therapeutic precursors may be released, or therapeutic manufacture unit 108 may produce active pharmaceuticals or biopharmaceuticals.

Therapeutic storage 412 may store excess medication produced by therapeutic manufacture 108. Medication can be stored rather than manufactured as needed if large doses, i.e., doses that cannot be made fast enough by therapeutic manufacture unit 108, are needed at time intervals.

Figure 4d shows basic components or interactions of sensor manufacturer 110. Systems-biology platform 104 sends software instructions to sensor manufacturer 110 to dictate manufacture, disassembly, activation, or deactivation of software-programmable biosensors. Once reconfigurable biosensors are programmed and produced, such components and sensor data signals are integrated, multiplexed, or processed

in combination into biosensor platform 102 for biological sensing.

Biosensor chip 421 acts as array or probe arranger 420 attaches probes onto the array. Probe arranger 420 may attach a probe for assaying, according to instructions by systems-biology platform 104. The method of attaching by probe arranger 420 can be a printing method (e.g., placing probes on array with automated machinery). Probes may be attached through microspotting, in which an automated microarray is produced by printing small quantities of pre-made biochemical substances onto solid surfaces.

The printing method may be ink-jet printing, e.g., GeSiM; a non-contact method places the probes on the array. In this method the probes are sprayed on a surface using piezoelectric or other propulsion to transfer biochemical substances from nozzles to solid surfaces, or directly placed. This method allows *in situ* synthesis, advantageously synthesizing oligonucleotides on-the-fly directly on the array surface. To change DNA that may be placed on the array, systems-biology platform 104 provides probe arranger 420 with a list of sequences to synthesize.

Another example of a technique usable probe arranger 420 is photolithography, e.g., from Affymetrix GeneChips. Photolithography allows olignucleotides to be built base-by-base (e.g, proteins build amino acid-by-amino acid) on the array surface by repeated cycles of photodeprotection and nucleotide or amino acid addition. In a manner similar to ink-jet printing, this process allows the building of M/N

arrays without pre-existing probes and can generate probes *in situ* on the surface of biosensor chip 421.

Customizable microarray platforms e.g., from CombiMatrix, including semiconductor-based desktop microarray platforms may fabricate custom oligonucleotide biochips. Microarrays with unique content are designed and fabricated on-the-fly using software driven process to generate reagents electrochemically. DNA oligonucleotides are synthesized *in situ* according to a desired probe sequence. Probe arranger 420 may use a cell-positioning chip, e.g., the Aviva chip, to provide living whole-cell arrays.

Optionally soft lithography may use a stamp to pattern surfaces of the array, using a patterned elastomer based on program instructions to define microfluidic networks on the surface.

Figure 5 shows DNA unit 500, representing the organization of sensors in biosensor platform 102, such as RNA sensor 202 (Figure 2), peptide or protein sensor 203 (Figure 2), etc. DNA unit 500 may include DNA sensor 201, DNA therapeutic manufacture 501, DNA therapeutic reservoirs 502, or DNA reconfigurable biosensor 503 together in the same physical structure, which lie in close proximity with each other. DNA therapeutic manufacture 501 is a structure-specific category of therapeutic manufacture 108 (Figure 1a, Figure 1b, Figures 4a to 4c). DNA therapeutic reservoirs 502 and DNA reconfigurable biosensor 503 are structure-specific categories of therapeutic reservoirs 109 and sensor manufacturer 110 (Figure 1a, Figure 1b, Figures 4a to 4c) respectively.

Sequential steps begin with input introduction into DNA unit 500, specifically DNA sensor 201. Raw data is transferred to systems-biology platform 104, a remote source. Systems-biology platform 104 processes information, outputting data and giving instructions to DNA therapeutic manufacture 501, DNA therapeutic reservoirs 502, and DNA reconfigurable biosensor 503. DNA therapeutic manufacture 501, DNA therapeutic reservoirs 502, and DNA reconfigurable biosensor 503 perform instructed tasks, with DNA sensor 201 monitoring respective progress.

DNA sensor 201 monitors or senses organism response to therapies dispensed by DNA therapeutic manufacture 501, DNA therapeutic reservoirs 502, or DNA reconfigurable biosensor 503. The proximity of DNA sensor 201, DNA therapeutic manufacture 501, DNA therapeutic reservoirs 502, or DNA reconfigurable biosensor 503 within the same unit facilitates monitoring from DNA sensor 201.

Ongoing feedback is transmitted from DNA sensor 201 to DNA therapeutic manufacture 501, DNA therapeutic reservoirs 502, and DNA reconfigurable biosensor 503, while responding continually to DNA sensor 201 raw data, creating a cyclic system of monitoring or responding.

Figure 6 is a flow chart showing automated or computer-assisted diagnosis of therapy recommendations or reports for a target host, which is identified initially for possible diagnosis or treatment 601. To determine whether the host will benefit from diagnosis or treatment, the host undergoes preliminary screening 602. Preliminary screening may be

implemented through a software form host undergoes preliminary modeling 603.

Modeling or simulation is used to model appropriate components or characteristics of a device. After preliminary modeling 603, the behaviour of the model is verified for accuracy 604. If the behavior of the model is not ok, biosensor 100 is modified 605, and preliminary modelling 603 is repeated. If the behavior of the model is ok 604, biosensor 100 is configured 606. A reconfigurable biosensor is made or programmed according to such a model.

The reconfigurable biosensor may be verified to comply or adhere to FDA regulations 607. If the biosensor does not comply or adhere, it is modified 608 and configuration 606 or verification of adherence to FDA regulations 607 is repeated. If the biosensor does comply or adhere to FDA regulations, it is implanted or attached to the host 609.

The biosensor is initialized to allow sensor or detection activity *in vivo* 610. Sensing or software is executed 611. Initialization of the biosensor and execution of sensing or software may operate in sequential order or in parallel. Once the biosensor and software is initialized, initial *in vivo* sensing begins 612. Sensor data is then used for *in vivo* modeling 613 via systems-biology platform 104. After *in vivo* modeling 613, biosensor 100 generates a diagnosis or therapy recommendation 614.

Therapy recommendations may result in commands to therapeutic unit 615 for therapeutic manufacturing or dispensing. Ongoing feedback between initial *in vivo* sensing

612, diagnosis or therapy recommendations 614, or commands to the therapeutic unit creates an automated sensing, modeling, and treatment cycle.

The foregoing descriptions of specific embodiments of the invention have been presented for purposes of illustration and description. They are not intended to be exhaustive or to limit the invention to the precise forms disclosed.

CLAIMS:

1. A multi-functional electronically configurable switching array coupled programmably to a plurality of different sensors including a DNA sensor, an RNA sensor, a peptide or protein sensor, an antibody sensor, an antigen sensor, a tissue factor sensor, a vector and virus vector sensor, a lipid and fatty acid sensor, a steroid sensor, a neurotransmitter sensor, an inorganic iron and electrochemical sensor, a pH sensor, a free radical sensor, a carbohydrate sensor, a neural sensor, a chemical sensor, a small molecule sensor, an exon sensor, a metabolite sensor, an intermediates sensor, a chromosome sensor, or a cell sensor.

2. Sensor apparatus according to claim 1 which is configurable electronically to couple or interconnect selectively to one or more biosensor signals from said sensors.

3. Sensor apparatus according to claim 1, further comprising a positioning chip.

4. Sensor apparatus according to claim 3 wherein the positioning chip comprises a patch clamp.

5. Sensor apparatus according to claim 1 including a peptide or protein sensor which comprises an electrophoresis tag or micro-assay, or protein chip.

6. Sensor apparatus according to claim 1 including an antibody sensor which comprises a phagotope biochip.

7. Sensor apparatus according to claim 1 wherein the sensor array includes a vector and virus vector sensor comprising a micro-array or assay with known sequence virus attached, or a micro-array or assay that detects homologues.

8. Sensor apparatus according to claim 1 including a carbohydrate sensor which comprises a glycochip, or a whole blood glucose monitoring system.

9. Apparatus according to claim 1 wherein the array includes a cell sensor comprising a bionic chip for cell-growth.

10. Sensor apparatus according to claim 1 further comprising a therapeutic unit comprising a micropump, a polymer scaffold comprising hydragel or an implantable bio-MEMs chip comprising a medication reservoir, said therapeutic unit being coupled to at least one sensor.

11. Sensor apparatus according to claim 1 wherein said array includes a DNA sensor comprising a micro-array or functional screen assay.

12. Sensor apparatus according to claim 10 further comprising a controller that controls the therapeutic unit.

13. Sensor apparatus according to any of the preceding claims, further comprising a systems biology platform arranged to analyse sensor data output from said switching array and to configure said switching array.

14. Biosensor apparatus substantially as described herein above with reference to Figure 2, optionally in conjunction with any of Figure 1A, Figure 1B, Figure 3A, Figure 3B, Figure 3C, Figure 4A, Figure 4B, Figure 4C, Figure 4D, Figure 5 or Figure 6 of the accompanying drawings.